"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

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EDITORIAL

Two outstanding events have made the inception of 1955 notable for British Anaesthesia. The decision by Her Majesty the Queen to honour Professor Macintosh has been received with pleasure by all his many friends. No one will question the statement that Professor Macintosh has contributed more than any other man to raising the standard of anaesthesia over the world as a whole. The influence of sound teaching which has emanated from the Oxford department and been widely dispersed through many excellent publications must have been felt wherever anaesthesia and surgery are practised. We offer Sir Robert Macintosh our felicitations and congratulations, and we wish him many years of active life in which he may enjoy his distinction.

The second important happening has been the establishment of a University department of Anaesthesia in Glasgow, which will be greeted with satisfaction by all members of the specialty. The formation of such departments not only provides for research into the many problems encountered in the specialty of anaesthesia, but also, as past experience as shown, raises the overall standard of anaesthesia in the area concerned. It seems not inappropriate to express the hope that other University centres, who have not yet seen their way to establishing such a department, will in the course of time follow the lead now set by Oxford, Newcastle, Leeds, Cardiff, Liverpool, Bristol, and Glasgow. We offer our most sincere congratulations and good wishes to Dr. Alex. C. Forrester as the first head of the department in Glasgow.

THERE can be no room for complacency among anaesthetists. The tools at our disposal are superior pharmacologically and mechanically to those which were at the disposal of our colleagues twenty years ago. Few will deny that the standard of education of anaesthetists, both as regards to the medical sciences and the specialty, has been very considerably raised during the past few years. The terms and conditions of service for consultant anaesthetists are better today than they have ever been in this country. Yet there is ample evidence that accidents still occur. One has only to regard the reports of the Registrar-General on deaths, or of the Committee of the Association of Anaesthetists of Great Britain and Ireland which is investigating deaths under anaesthesia (1952; Pask, 1955), to be convinced that all is not well nor perhaps even as good as it could be. Although there have been indications in the medical press that the Anaesthetists of Great Britain do not consider that their statistics would tell the same rather alarming story as those recently reviewed by Beecher and Todd (1954) in America, yet no one in these islands has yet produced a comparable series of anaesthetics investigated with the same thoroughness and impartiality and on the same scale. This must be regarded as a calamity and it is to be hoped that some effort will be made to combine the great facilities for this type of investigation, which should exist in the several anaesthetic departments in this country. In the meantime we must be contented with the investigation being carried on by the Association of Anaesthetists. It is abundantly clear that this is by no means comprehensive, and that there are areas in the country, including some leading centres, which are still not supporting this investigation in the wholehearted manner it deserves. If we are not prepared to help to the extent of filling in forms supplied by our own Association and repeating anonymity, it will not be surprising if the administrators of the National Health Service feel tempted to step in and carry out their own investigation.

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LIVER FUNCTION AFTER SURGERY

A Study of 50 cases with particular reference to Serum Cholinesterase

BY

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CONSIDERABLE changes have occurred during the last few years in the practice of surgery, largely due to the development of new anaesthetic agents, in particular the group of relaxant drugs. During the same period advances have been made in methods of estimating hepatic function. It is now recognized that a series of tests, repeated at intervals over a period of time, gives a more valid impression of liver function, which is essentially a dynamic process, than isolated observations which only indicate function at the moment of testing. There is much interest in serum cholinesterase as an index of liver function, especially since easily performed and reliable methods have become available for its estimation. Final assessment of the sensitivity of the test is not yet complete. The following report analyzes liver function during the first 14 days after operation performed under modern anaesthesia. An effort has been made to integrate serum cholinesterase with a group of tests of liver function chiefly concerned with protein metabolism.

MATERIALS AND METHODS

A series of 50 patients undergoing operation in the Professorial Surgical Unit was chosen for study, the selection being made on grounds of convenience. In general, cases of major operation were chosen since they seemed more likely to produce changes. Table I indicates the range of procedures investigated; 34 of the operations were considered major and 16 minor. No death occurred in the series.

TABLE I

Operation	Number of Cases
Partial gastrectomy	11
Gastro-enterostomy	2
Cholecystectomy	4
Appendicectomy	2
Operations of the colon	3
Excision of the rectum	2
Laparotomy	1
Minor rectal operations	4
Nephrectomy	1
Prostatectomy	2
Various operations for hernia	7
Thyroidectomy	3
Operations on neck glands	5
Radical mastectomy	2
Amputation of leg	1
TOTAL	50

No attempt was made to influence the choice of anaesthetic, so that the series represents a random sample of anaesthesia currently used in the Unit. The duration of the operation, and the type and amount of anaesthetic agent used were recorded, with a clinical estimate of the blood loss and the patient's general condition at the end of operation. Blood samples were obtained for serum analysis before and

after the operation, on the morning of the first post-operative day, and every second morning thereafter for 14 days. Estimations on these samples included thymol turbidity, zinc turbidity, cephalin cholesterol flocculation, and serum cholinesterase. Thymol turbidity was estimated by the method of Ducci (1947) in which copper sulphate standards are used. Zinc turbidity was recorded as described by Kunkel (1947). Cephalin cholesterol flocculation was carried out in the original manner (Hanger, 1939). Serum cholinesterase was estimated by the electrometric method (Michel, 1949) whereby acetylcholine bromide is hydrolyzed by the enzyme in a buffered solution with the liberation of acetic acid. The drop in pH over an hour was noted and the results expressed as ΔpH units per hour. All estimations were done in duplicate and the method found to be reliable and relatively uncomplicated. In a consecutive series of 231 estimations done in duplicate with incubation over the period of one hour, the duplicates gave identical readings in 32.4 per cent, a difference of 0.02 pH unit was found in 52.8 per cent, and a difference of 0.04 pH unit in 14.6 per cent. Essential requirements were an accurate pH meter and a water bath which could be maintained at 25°C.

In addition, in 20 cases in the series, parallel estimations were made of the daily urinary urobilinogen output (Schwartz, Sborov and Watson, 1944), in order that another aspect of liver function might be available for comparison with the results of the serum cholinesterase estimations.

TABLE II

Adjusted mean values for 50 cases.

Time of observations	Zinc turbidity	Thymol turbidity	Serum cholinesterase
	Adjusted mean	Adjusted mean	Adjusted mean
Pre-operation	1.13	0.64	0.94
Post-operation	1.12	0.61	0.90
+ 1 day	1.04	0.56	0.91
+ 3 days	1.00	0.54	0.80
+ 5 days	0.95	0.53	0.74
+ 7 days	0.97	0.57	0.74
+ 9 days	1.04	0.64	0.74
+ 11 days	1.05	0.69	0.80
+ 13 days	1.07	0.62	0.74

Zinc and Thymol turbidity in logarithmic units.
Serum cholinesterase in Δ pH units/hr.

RESULTS

The primary object of the investigation was to discover whether any general post-operative change occurred in the group of tests, and, if so, whether it could be related in any way to the various factors involved, principally the operation and the anaesthetic. The results of the serum cholinesterase and the thymol and zinc turbidity estimations were analyzed statistically. It was found that, in the case of the zinc turbidity, experimental error was not normally distributed in that the error variance increased in the group of higher readings. Accordingly logarithmic values have been used to eliminate this factor. For consistency these have also been used in the case of thymol turbidity.

Analyses showed that on the average there was a fall in the zinc and thymol turbidities reaching a minimum value 5 days after operation and thereafter the values rose again. The differences between the mean levels were significant at a level of $P < 0.1$ per cent. There was a similar fall in the cholinesterase results but no comparable rise. The differences were again significant. A graphic representation of the adjusted mean values for

all 50 cases is given in figure 1. It is seen that in the case of all three tests only a minor alteration occurred in the course of the operation, but was followed by a fall as described above. By the thirteenth post-operative day the serum cholinesterase was still notably below the pre-operative mean value. It was unfortunately not possible to follow a sufficient number of cases for a longer period of time to establish the time taken for a return to pre-operative levels.

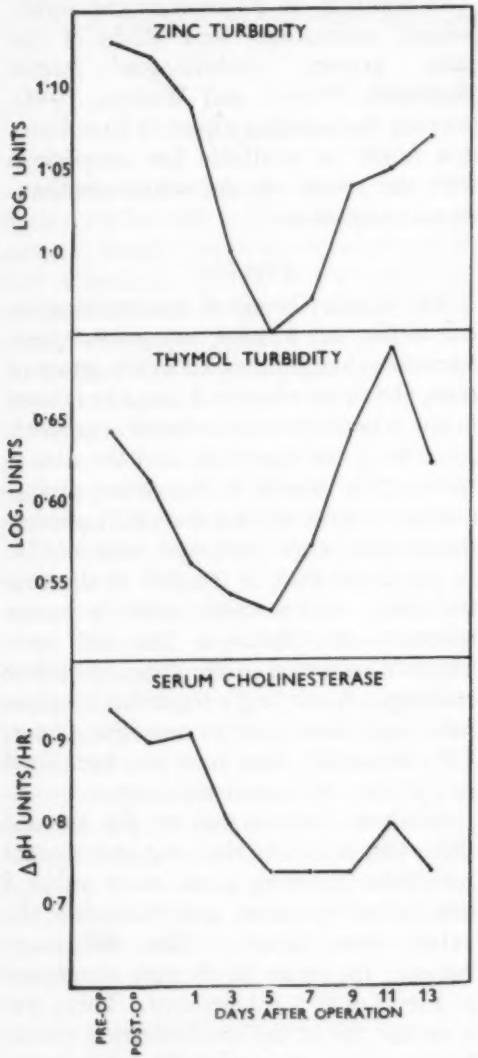

FIG. 1

Post-operative variation in zinc turbidity, thymol turbidity and serum cholinesterase. Adjusted mean values for 50 cases.

The changes described could not be correlated in any way with the age or sex of the patient, the duration of the operation, or the blood loss incurred. Some difficulty was found in interpreting the effects of the operation or anaesthetic on the trend of results owing to the relatively small number of cases of the various procedures and the current tendency to use several anaesthetic agents in each case.

Following what appeared to be different degrees of the post-operative trend of results as described, the 50 cases were accordingly grouped as shown in table III. Particular attention was paid to the groups of upper abdominal cases in general, peptic ulcer in particular, and to the effect of the relaxants, and analyses of the zinc turbidity and cholinesterase were carried out. Adjusted mean values for the various groups are given in table IV. With regard to cholinesterase, no statistically significant differences in post-operative trend were found in the results, either between upper abdominal cases and others or among the various anaesthetic groups. However, it was noted that all 16 cases who received a relaxant but neither ether nor trichlorethylene had a fall of > 30 per cent in serum cholinesterase from the preoperative value; only 31 of the total 50 cases, and only 4 out of 10 cases receiving ether alone, showed this fall. No correlation could be obtained between the

TABLE III

Grade of Operation	Grouping by Region and Pathology	ANAESTHETIC (a) Gallamine Triethiodide No Ether or Trilene		(b) Ether only		(c) No Ether Miscellaneous		(d) Ether + Relaxants	
		Male	Female	Male	Female	Male	Female	Male	Female
Major	Upper Abdominal								
	Ulcers	2	—	—	—	—	1	8	2
	Cancers	—	—	—	—	1	1	1	2
34	Others	—	1	—	1	—	—	—	1
	Other Regions								
	Cancers	1	—	—	1	1	1	1	2
	Others	1	1	—	3	1	—	—	—
Minor 16	Miscellaneous	1	2	3	2	2	3	1	2

All cases except one were induced with thiopentone, and were given nitrous oxide and oxygen.

TABLE IV

Adjusted mean values for various groups of cases

	Times of observations								
	Before Operation	After Operation	+1 Day	+3 Days	+5 Days	+7 Days	+9 Days	+11 Days	+13 Days
ZINC TURBIDITY									
Upper abdominal	1.03	1.03	0.93	0.87	0.86	0.86	0.95	0.96	0.99
Others	1.21	1.19	1.12	1.10	1.02	1.05	1.11	1.11	1.12
Male peptic ulcers	1.11	1.10	0.97	0.86	0.83	0.81	0.92	0.94	1.01
Others	1.14	1.13	1.05	1.04	0.98	1.01	1.08	1.08	1.08
Anaesthetic group (*a*)	1.25	1.24	1.23	1.12	1.06	1.08	1.10	1.10	1.08
,, ,, (*b*)	1.31	1.28	1.24	1.23	1.18	1.21	1.22	1.22	1.28
,, ,, (*c*)	0.95	0.96	0.83	0.80	0.78	0.80	0.91	0.90	0.91
,, ,, (*d*)	1.08	1.07	0.96	0.95	0.88	0.89	1.01	1.05	1.05
SERUM CHOLINESTERASE									
Upper abdominal	0.88	0.84	0.83	0.71	0.68	0.67	0.68	0.73	0.67
Others	0.99	0.95	0.98	0.86	0.82	0.78	0.78	0.85	0.80
Anaesthetic group (*a*)	0.93	0.76	0.87	0.72	0.65	0.64	0.62	0.76	0.75
,, ,, (*b*)	1.01	1.00	1.02	0.91	0.84	0.86	0.89	0.88	0.89
,, ,, (*c*)	1.01	0.99	0.96	0.84	0.80	0.75	0.68	0.83	0.68
,, ,, (*d*)	0.88	0.88	0.86	0.75	0.75	0.71	0.76	0.74	0.73

Zinc turbidity in logarithmic units.
Serum cholinesterase in Δ pH units/hr.

maximum fall and the dosage of thiopentone or gallamine triethiodide, or both in summation. The use of suxamethonium at the end of an operation did not cause a significant drop in circulating cholinesterase level from that existing before the operation.

The zinc turbidity results showed a significant difference between the group of male peptic ulcers undergoing partial gastrectomy and all other cases in that the post-operative dip about the fifth day was more pronounced ($P<0.01$). There was also a difference in respect to the anaesthetics—the gallamine group (*a*) delayed its post-operative dip until the third day and failed to rise with the others.

Cephalin Cholesterol Flocculation.

Eighteen cases developed a positive cephalin cholesterol flocculation after operation; 12 commenced between the fifth and tenth days, but only 9 of the 18 had positive reactions on two or more occasions. These are recorded in table V, with information about the other tests at the time of the positive reaction. It can be seen that all affected cases had abdominal operations, and in most instances a post-operative complication occurred or other factors were present such as infection, poor general nutritional state, or multiple secondaries were present in the liver. A high correlation was present between a positive flocculation and a low cholinesterase.

Urinary Urobilinogen.

Serial estimations of total daily urinary urobilinogen output carried out in the post-operative course for the first 20 cases showed significant increases in 15 cases. The peak occurred on varying days between the third and tenth, and was followed by a fall to normal by the twelfth or fourteenth day. A specific reason for the rise was suspected in 2 cases, namely, absorption from a haematoma at the operation site. In the remaining 13 the cause was inferred to be an inability of the liver to deal with urobilinogen in the normal entero-hepatic circulation. It was noted that a fall in turbidity and cholinesterase broadly coincided with an increase

TABLE V

Cases developing a positive cephalin-cholesterol flocculation post-operatively.

Case	Operation	Remarks	Zinc	Thymol	Cholinesterase
4	Partial gastrectomy	Post-op. biliary fistula: blood transfusion	Normal	High	Low
19	Cholecystectomy	Recent attack acute cholecystitis	Normal	Normal	Low
26	Partial gastrectomy	Acute dilatation of stomach	Normal	Normal	Low
33	Anterior resection of rectum	Wound dehiscence	Slight increase	Normal	Very low
37	Anterior resection of rectum	Multiple secondaries in liver	Slight increase	High	Low
43	Gastro-enterostomy	General nutrition very poor	Normal	Normal	Low
46	Colo-colic anastomosis	Multiple secondaries in liver	Normal	Normal	Low
49	Cholecystectomy, separation of adhesions	Old case of diverticulitis	Normal	Slight increase	Low
50	Prostatectomy	———	Normal	Normal	Low

in urobilinogen, this being more marked in the major cases.

DISCUSSION AND CONCLUSIONS

The most striking feature of the results was the post-operative trend in the turbidities and the serum cholinesterase. Vorhaus and Kark (1953) have shown that although the serum cholinesterase has a wide range of normality, each individual has his own normal level within this range, which does not vary. This has also been our experience; in 8 patients, not subjected to operation, observations were made every second day for 14 days, and variation was within 0.1 pH unit. Over this period thymol turbidity was fairly constant and zinc turbidity only a little less so. The present investigation may well indicate that there is a depression in liver function post-operatively, most marked about the fifth day, and that the serum cholinesterase is a sensitive indication of this. It is supported by the auxiliary urobilinogen results dealing with another aspect of liver function. Serum cholinesterase appears to originate in the liver and to be very closely associated with albumin synthesis. The post-operative fall in circulating serum cholinesterase may be related to several other factors: (1) lack of essential amino acids from reduced intake; (2) loss by exudation at the site of operation greater than can be concurrently replaced; (3) dilution in the circulating plasma in the fluid changes occurring after operation. In many of the cases, post-operative protein starvation was not a factor, and loss at the operation site seemed unlikely. Dilution was unlikely as the percentage falls in the level of the two turbidities and the serum cholinesterase which occurred in the days after operation varied very considerably when these falls were compared in individual cases.

It has been suggested (Wilkinson, Billing, Nagy, and Stewart, 1950) that the post-operative change in protein metabolism shown by an increased urinary nitrogen excretion is partly due to an increased protein katabolism closely associated with operative trauma. The mechanism of this is not yet clear; it seems possible that the turbidity and cholinesterase changes are another aspect of the same problem. Zinc turbidity is most probably a reflection of the gamma globulin concentration of the plasma while thymol turbidity very likely depends on the plasma pattern of the beta and gamma globulins and some part of the lipoid fraction. A fall from the individual normal levels of the turbidities may well result from a change in the plasma globulin pattern arising from hepato-cellular dysfunction in the formation of the globulins; it may be, therefore, that in interpretation of turbidity tests done serially on a patient, either a decrease or the more commonly seen increase in value from the individual normal can indicate liver dysfunction. If this is not so, the only significant finding is the post-operative fall in cholinesterase levels; this would indicate the serum cholinesterase to be the most sensitive test in the group.

Another possible interpretation of the results is that the turbidity tests of liver function ought not to be used in the post-operative or post-traumatic state when katabolic changes are in process owing to the alterations occurring in the plasma globulins which do not necessarily imply liver dysfunction.

SUMMARY

A study of liver function after operation was carried out in a series of 50 cases. The tests used were serum cholinesterase, thymol turbidity, zinc turbidity, cephalin cholesterol flocculation, and, in 20 of the cases, quantitative urinary urobilinogen. Observations were made before and after operation and on every second day for 14 days.

No change was found immediately after operation, but a fall occurred later in the serum cholinesterase and the two turbidity tests, the lowest values being reached on the fifth post-operative day. It is suggested that a mild hepato-cellular dysfunction occurred and that the serum cholinesterase was a sensitive indicator of this change. Nine cases developed a positive cephalin cholesterol flocculation. All of these showed concurrent low values for serum cholinesterase. Alteration in the normal pattern of liver function may be indicated either by a rise or a fall from the normal level of the zinc and thymol turbidity, but the turbidity tests are possibly unreliable indicators of liver function in the post-operative phase.

No definite evidence was found of the part played by any particular operative procedure or by any anaesthetic agent in producing the observed post-operative changes, but further investigation of the relaxants is suggested.

ACKNOWLEDGMENTS

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THE ACTION OF LAUDEXIUM IN MAN AND EXPERIMENTAL ANIMALS

BY

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THE drug laudexium methylsulphate (Laudolissin) was developed as a result of the researches of Taylor and Collier (1950 and 1951) into the relationship of chemical structure and pharmacological activity among myoneural blocking agents. It has received several clinical trials (Bodman, Morton and Wylie, 1952; Binning, 1953; Sara, Marshall and Balthasar, 1954) and has been reported to be a completely satisfactory substitute for d-tubocurarine in anaesthesia. Just lately, however, after an investigation of a large series of cases, Dundee, Gray and Riding (1954) have had occasion to question this conclusion. Early in 1953 the author carried out a clinical study of the action of laudexium. Some of the results of that work indicated that the action of this drug might differ in some respects from that of d-tubocurarine, with the result that a re-investigation of its properties in experimental animals was undertaken. This paper is an account of the clinical study and of the experimental work to which it led.

CLINICAL STUDIES

Methods

Patients were premedicated with omnopon gr. 1/3 (20 mg.) and scopolamine gr. 1/300 (0.2 mg.) if they were between the ages of 16 and 60, and with morphine gr. 1/6 (10 mg.) and atropine gr. 1/100 (0.6 mg.) if they were older. Anaesthesia was induced with thiopentone or thialbarbitone (Kemithal) and an endotracheal tube passed. Nitrous oxide and oxygen were then administered in the proportions of 6 : 2 l. per minute in a semi-closed system; pethidine and, if necessary, additional barbiturate were used as supplements. In all, 86 cases were studied.

The types of operation performed are shown in table I, and their approximate duration in table II. The methods of intubation used are given in table III. An initial dose of 10 mg. of laudexium was given in each case, and thereafter the drug was injected in 10-mg. increments until the abdomen relaxed or, where this was necessary because the chest was to be opened, until artificial respiration was readily performed. In the vast majority of patients, relaxation for the entire operation, including abdominal closure, was produced by laudexium.

TABLE I

The type of operation performed

Operation on	No. of cases
Stomach	14
Gall bladder and bile ducts	17
Appendix and colon	13
Other viscera	12
Prostate gland	4
Total abdominal operations	60
Major thoracotomy	14
Thoracoplasty	12
	86

TABLE II
The duration of the operations

ABDOMINAL OPERATIONS

Duration of operation (minutes)	No. of cases
0– 30	5
31– 60	23
61– 90	15
91–120	9
121–150	3
150 +	4
	59

1 case not completed under laudexium

CHEST OPERATIONS

	Average duration (minutes)	No. of cases
First stage thoracoplasty	100	8
Second stage thoracoplasty	60	4
Major thoracotomy	240	14
		26

TABLE III
The technique of intubation

Method of intubation	No. of cases
Local anaesthetic spray	2
With suxamethonium	40
With gallamine triethiodide	44
	86

Results

Dosage.

As in previous studies of "curarizing" agents the potency of laudexium was estimated by determining the dose which would produce enough relaxation for the opening of the abdomen during a laparotomy. In those who had received suxamethonium, or had been intubated with a local anaesthetic spray, this was 28.9 ± 8.7 mg. The comparable amount of d-tubocurarine had already been found to be 17.2 ± 7.7 mg. (Hunter, 1952). Where gallamine triethiodide was used for intubation, 18.3 ± 11.3 mg. of laudexium was required to relax the abdomen. This small amount was no doubt due to the fact that the action of the gallamine had not completely worn off by the time at which the laudexium was given, viz. 15 to 25 minutes after intubation. There was thus a marked summation of the effects of these two agents (cf. Dundee *et al.*, 1954).

There was some variation in the duration of a single dose, but the mean amount required for periods of relaxation lasting half an hour or less was virtually the same as that needed to induce abdominal relaxation (table IV). In cases where the relaxation was maintained for 31 to 45 minutes, the total amount of the drug given exceeded this amount by 13 to 14 mg. showing that additional doses were required if the period of relaxation was to be extended.

The numbers in the groups where yet longer periods of relaxation were required are too small for detailed analysis. Over all, however, in 15 patients undergoing major upper abdominal operations and intubated while under the influence of

TABLE IV
The dose of laudexium
(The numbers in brackets indicate the range of doses)

Purpose	Method of intubation: Suxamethonium or spray (mg.)	Method of intubation: Gallamine Triethiodide (mg.)
To relax abdomen	28.9 ± 8.7	18.3 ± 11.3
For relaxation lasting up to 30 minutes	26 (range 20–30)	15 (range 10–20)
For relaxation lasting 31–45 minutes	40 (range 25–50)	28 (range 20–30)
For major upper abdominal operations (mean duration of relaxation 73.5 minutes)	—	42.3
For major chest operations (mean duration of relaxation 193 minutes)	—	50.3

gallamine triethiodide, 42.3 mg. of laudexium were required for an average of 73.5 minutes of relaxation. By contrast, in 14 major thoracotomies where laudexium was used to facilitate artificial respiration, a mean amount of 50.3 mg. was used over 193 minutes. This low rate of dosage during chest operations does not indicate any special virtue on the part of laudexium. It has also been noted when d-tubocurarine has been used in such cases.

Action on Respiration.

Like all " curarizing " drugs, laudexium produced paralysis of the respiratory muscles. As Dundee and his colleagues (1954) remarked, so in this series too, it was found to be very easy to take over the patient's breathing, even when respiratory movements were still present. There was, however, one important difference between the action of laudexium on the breathing, and that of other neuromuscular blocking agents. With other drugs it was possible in an appreciable number of cases to obtain abdominal relaxation without depressing respiration to the point at which manifest anoxia or hypercarbia developed. With laudexium it was rarely possible to do this. Indeed, in some cases, in the presence of an apparently adequate though reduced respiratory excursion, the signs of obvious respiratory insufficiency appeared. There was never any evidence of bronchospasm in these cases to account for the failure of ventilation, but in two instances there was a considerable increase in the amount of bronchial secretion. It is possible that this interfered with air entry into the lungs in the cases where oxygenation failed in the presence of apparently adequate respiratory displacement. In this connection it is interesting that Collier and Macauley (1954) have shown that laudexium increases secretion from the related salivary glands in cats.

Circulatory Effects.

Some quite marked changes in the blood pressure occurred when laudexium was given. These are shown in table V. Most of the rises were asphyxia , and traceable to the marked interference with respiratory function produced by the drug. The falls in the blood pressure, however, seemed to be a specific effect of the agent. They appeared in poor risk cases, and only after the first dose of the drug. No special treatment for this hypotension was necessary, and it rarely persisted for more than 10 minutes.

Antagonism by Neostigmine.

As the patients were anaesthetized by a method which allowed nearly complete recovery of consciousness within a few minutes of withdrawing the anaesthetic, it was possible to assess fairly accurately the effectiveness of neostigmine as an antidote. If, after its administration normal breathing was fully restored, the patient was able to cough effectively on his tube, and he could, when asked to do so, open his eyes and keep them open, decurarization was regarded as complete. If his eyelids tended to droop, if the coughing produced by moving the endotracheal tube was ineffective, or if intercostal paralysis or chin tugging persisted, it was considered that decurarization had failed.

Neostigmine was given to 68 patients in doses of 1.25 mg. or 2.5 mg. with the amounts of atropine recommended by Hunter (1953) to prevent muscarinic effects. It early became apparent that,

TABLE V
The blood pressure changes after the administration of laudexium

Blood pressure rise	−10 mm.	−20 mm.	−30 mm.	−40 mm.		
Number of cases	2	1	3	2		
Blood pressure fall	−10 mm.	−20 mm.	−30 mm.	−40 mm.	−50 mm.	−60 mm.
Number of cases	13	11	2	3	1	1
Blood pressure unchanged			31 cases			
No record			15 cases			

though the smaller of these doses would quickly abolish mild respiratory depression due to d-tubocurarine or gallamine triethiodide, it was often ineffective against that due to laudexium. There were, however, cases in which 2.5 mg. of neostigmine was incompletely effective, and in one instance even a total of 3.75 mg. of this drug failed to produce the desired response (table VI). There are no comparable figures for d-tubocurarine, but only once in the course of several hundred administrations of this relaxant drug have I failed to obtain a complete reversal of paralysis with neostigmine.

These clinical results raised some interesting problems which were further investigated in the experimental laboratory.

EXPERIMENTAL STUDIES

Methods

The effects of laudexium on the breathing were studied on 5 cats anaesthetized with pentobarbitone given by intraperitoneal injection in a dose of 40 mg./kg.; adequate maintenance doses of this drug were subsequently given by the intravenous route. Respiration was recorded by tambours placed on the chest and abdomen. The mean blood pressure was taken with the aid of a mercury manometer connected by a column of citrate to one carotid artery. Restoration of normal breathing after its paralysis by laudexium was the criterion of successful antagonism.

Antagonism in mice was studied on a simple survival basis. Drugs were given either by intraperitoneal or intravenous injection to mice weighing 18–40 g. By neither route did the volume given exceed 0.21 ml.

Results

Cats. Laudexium was given in the dosage necessary to produce profound respiratory depression or apnoea (usually 100 γ/kg.) on seven occasions 0.1 mg./kg. of neostigmine given immediately thereafter either failed to produce any response or gave rise only to a partial restoration of breathing. Even with 0.2 mg./kg. of neostigmine, complete reversal of the paralysis was obtained in only one animal, though this amount had always proved effective in reversing paralysis produced by d-tubocurarine and gallamine triethiodide.

Physostigmine in a dose of 0.12 mg./kg. with an equal amount of atropine was also tested as an antidote. Though this dose of the drug produced fasciculation and fibrillation of voluntary muscle when administered to the normal animal, it did not produce any apparent reversal of respiratory depression due to laudexium. Physostigmine, however, may have been too slowly acting an antidote to be effective on such a test, though in a control study with gallamine triethiodide some evidence of recovery was observed.

In one animal the sciatic nerve was stimulated while laudexium was acting, and there was observed a phenomenon which had a parallel in the human sub-

TABLE VI
The effect of neostigmine on laudexium paralysis

Degree of decurarization	Complete	Doubtful	Failed	None given
Number of cases	46	8	14	14
Incomplete records 4				

ject. During the administration of this drug in clinical anaesthesia it had been noted that breathing often became inefficient before abdominal relaxation occurred. It was found in the cat that apnoea appeared while the response of the unloaded foreleg muscles both to a single twitch and to a tetanus had scarcely been impaired.

Mice. An attempt was made to obtain additional information on these matters by studies in mice. It was shown that 0.3 mg./kg. of neostigmine with an equal amount of atropine given by intraperitoneal injection produced an appreciable reduction in the toxicity of gallamine triethiodide given intravenously in doses of 5.0 mg./kg. This dose of neostigmine was apparently ineffective in reducing toxicity of 0.25 mg./kg. of laudexium (table VII). It was, however, possible to demonstrate protection against laudexium in a larger dose (0.4 mg./kg.) by 0.2 mg./kg. neostigmine with 0.2 mg./kg. of atropine given intravenously in the same syringe.

The degree of protection obtained was not, however, so great as that which could be conferred against a comparable amount of gallamine triethiodide (table VIII). It was intended to study the corresponding antagonism with physostigmine, but the control tests with gallamine were so unpromising that the experiment with laudexium was not performed (table IX).

One other study was made. At the time when this work was done, the author

TABLE VII

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Laudexium	0.25	i.v	14	6*
Neostigmine	0.3	i.p.	6	6
Atropine	0.3			
Neostigmine	0.3	i.p.	6	3*
Atropine	0.3			
Laudexium	0.25	i.v.		
5 minutes later				
Neostigmine	0.3	i.p.	8	7†
Atropine	0.3			
Gallamine triethiodide	5.0	i.v.		
5 minutes later				
Gallamine triethiodide	5.0	i.v.	8	1†

* $X^2=0.025$ $P<0.9>0.8$
† $X^2=6.25$ $P<0.02>0.01$

TABLE VIII

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Laudexium	0.3	i.v.	5	2
Laudexium	0.4	i.v.	15	0*
Laudexium	0.4	i.v.	17	8*
Neostigmine	0.2			
Atropine	0.2			
Neostigmine	0.2	i.v.	6	6
Atropine	0.2			
Gallamine triethiodide	3.0	i.v.	7	4
Gallamine triethiodide	5.0	i.v.	8	0†
Gallamine triethiodide	5.0	i.v.	8	8†
Neostigmine	0.2			
Atropine	0.2			

* $X^2=7.07$ $P<0.01$ † $X^2=12.25$ $P<0.01$

TABLE IX

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Physostigmine	0.2	i.v.	9	9
Atropine	0.4			
Physostigmine	0.2	i.v.	5	1
Atropine	0.4			
Gallamine triethiodide	5.0			
Physostigmine	0.5	i.v.	6	6*
Atropine	0.5			
Physostigmine	0.5	i.v.	8	4*
Atropine	0.5			
Gallamine triethiodide	5.0			

* $X^2=3.00$ $P<0.10>0.05$

believed that if antagonism could be demonstrated between a curarizing drug and a depolarizing blocking agent, the former could be regarded as a competition blocker. Mice which had survived the administration of 0.25 mg./kg. of laudexium were given 1.8 mg./kg. Ro 3-0386, which is approximately the L.D. 95. An appreciable number survived (table X).

TABLE X

Drugs	Dose given mg./kg.	Route of injection	Mice used	Mice survived
Ro 3-0386	1.8	i.v.	7	0
Laudexium	0.2	i.v.	5	4
Ro 3-0386	1.8	10 minutes later		

* $X^2=5.2$ $P<0.05$ $P>0.02$

DISCUSSION

The results of the clinical study here reported confirm the conclusions reached by Dundee and his co-workers (1954) indicating, as they do, that laudexium cannot be used on all occasions in place of d-tubocurarine, chiefly because the paralysis produced by it is not completely reversed by neostigmine. In this study also, two minor defects of laudexium have come to light, namely, its peculiarly marked tendency to interfere with the breathing and its hypotensive action. These would not, however, be insuperable drawbacks to the use of the drug in clinical anaesthesia. Respiratory depression is readily rectified by artificial ventilation of the lungs and the fall in blood pressure noted was rarely serious and always evanescent.

The differences in the conclusions reached here and confirmed by Dundee and his colleagues (1954) from those of other workers are probably traceable to two factors. First, the depth of the anaesthesia obtained from nitrous oxide and oxygen given with a non-volatile supplement is never more than Plane 1 of Stage III of the Guedel classification. In consequence the whole of the relaxation for abdominal operations must be provided by a myoneural blocking agent. Not only so, in such cases deep " curarization " must be maintained until the abdomen has been closed. If volatile supplements to nitrous oxide and oxygen are employed, or if cyclopropane is used for anaesthesia, a relatively lighter plane of curarization will provide equally good relaxation, and very often it will be possible to close the abdomen without an additional dose of relaxant, especially if the anaesthesia is deepened at this time. In such cases antidote drugs are not often necessary. When they are given they are used to reverse a less profound myoneural block than exists in those who have received only Plane 1 nitrous oxide and oxygen anaesthesia. The apparent failure of the author and of the Liverpool team to obtain effective reversal of laudexium by neostigmine is therefore not an insuperable obstacle to the use of the drug. It is merely an indication that this agent, like decamethonium, requires for its successful administration a little more profound general anaesthesia than is necessary when d-tubocurarine or gallamine triethiodide is being given. Alternatively, it is an indication that, as in Binning's cases (1953), suxamethonium should be used to provide relaxation for abdominal closure.

Many of the differences between the author's experimental results and those of Collier and Macauley (1952) are also related to differences in the anaesthesia employed. It had been found in a previous study of decamethonium (Hunter, 1950) that the findings of the animal work

carried out under pentobarbitone were more applicable to the clinical administration of that relaxant by the technique outlined above than were those of Paton and Zaimis (1949) who used chloralose. Similarly in the present study, the results obtained from investigations on animals under pentobarbitone anaesthesia have given results approximating more closely to those obtained under clinical conditions than do those of Collier and Macauley (1952) who also used chloralose.

Other differences in the experimental results from those of Collier and Macauley (1952) are traceable to diversity of method. These workers demonstrated the antagonism between laudexium and neostigmine by a reversal of the dose which caused loss of the righting reflex in rabbits, that is, in animals only very lightly curarized. Collier and Macauley also found an antagonism in cats presumably from experiments with an isometric myograph. In this instrument also, truly complete paralysis is rarely induced, especially if the muscle is loaded. By contrast, the dose of a myoneural blocking agent which produces apnoea in a cat or mouse represents an amount which will inhibit more or less completely all conduction at myoneural junctions. It is, therefore, not surprising that neostigmine proved ineffective then, though it was apparently a satisfactory antidote at the lighter levels of curarization.

Finally it must be emphasized that though the experimental results here reported are in accord with the conclusions reached in the clinical investigation, the technique of anaesthesia used for this differed from those employed in the earlier studies of laudexium. It therefore seems that, when the usefulness of any curarizing drug is being assessed in the laboratory, it is desirable not merely to carry out experiments to show what are its general properties, but also to investigate the drug to find out whether it is likely to give the best results when combined with very light nitrous oxide and oxygen anaesthesia, or whether it will probably be more satisfactorily given at the slightly deeper plane of narcosis obtained with cyclopropane or other similar methods.

SUMMARY

(1) Laudexium was used to produce relaxation in 86 patients anaesthetized by nitrous oxide and oxygen with a non-volatile supplement.

(2) It provided satisfactory relaxation during the operation, but the paralysis could not always be reversed by neostigmine.

(3) It had a profound effect on respiration and sometimes lowered the blood pressure, though only for a short period.

(4) In a subsequent laboratory investigation neostigmine was not completely effective as an antagonist to laudexium in the cat and mouse.

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ANAESTHESIA WITH HYPOTENSION FOR FENESTRATION*

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THIS paper is a report on a small series of cases of anaesthesia for fenestration of the labyrinth in which a technique of "planned hypotension" was used.

THE OPERATION

The object of the fenestration operation is to overcome the obstruction offered to the transmission of sound-actuated waves by the fixation of the footplate of the stapes in the oval window by osteosclerotic bone. This is achieved by providing an opening in the wall of the bony labyrinth that will allow free movement of labyrinthine fluids in response to transmitted sound waves (Cawthorne, 1952). This was described as a one-stage endaural procedure by Lempert (1938).

The operation itself falls naturally into two parts (Hall, 1945): (1) the preparation of the middle ear, i.e. essentially a modified radical mastoidectomy; and (2) the trephining of the bony labyrinth, which is carried out under low-power magnification. The fenestra is then covered with a skin flap which is rotated from the wall of the external auditory meatus in continuity with tympanic membrane. The entire procedure in the present series occupied about four hours.

ANAESTHETIC REQUIREMENTS

The anaesthetic requirements for this operation are: (1) a smooth light anaesthesia of prolonged duration; and (2) the absence of bleeding, which may occur (*a*) during the incision from skin and soft tissues, (*b*) during the mastoidectomy from bone, and (*c*) during the actual trephining of the labyrinth from bone or from the skin flap.

It will be appreciated that, when working on the bony labyrinth under magnification, even a minute amount of haemorrhage will cause embarrassment to the surgeon—and, indirectly, to the anaesthetist! However, bleeding at this stage will not only render difficult—or, as has happened, impossible—the technical accomplishment of the operation: bleeding into the fenestra may well jeopardize a successful result by causing a post-operative serous labyrinthitis (Hughes, 1951) and subsequent closure of the fenestra, a not infrequent complication. In this connection, Gillies (1953) states that "the success of a procedure such as fenestration for otosclerosis depends largely on an

* This paper was awarded the Registrars' Prize for 1954 by the Scottish Society of Anaesthetists and was read before that body at Dunblane on April 3, 1954. The work was carried out at the Ear, Nose and Throat Hospital, Glasgow.

ischaemic field of operation and the absence of reactionary haemorrhage and clot formation afterwards." In another article (Gillies, 1950) he reviews the relationship of anaesthetic factors to surgical haemorrhage.

PHYSIOLOGICAL AND PHARMACOLOGICAL CONSIDERATIONS

The factors influencing the degree of haemorrhage from a wound are:

(1) The arterial blood pressure which varies as the product of the cardiac output and the peripheral resistance.
(2) The local venous pressure, which is to some extent dependent on gravity, and can therefore be influenced by posture
(3) The state of the peripheral capillaries, which is related to the carbon dioxide tension of the blood.
(4) The mechanism of blood clotting.

Although each must receive due consideration, it is with the first of these factors that we are chiefly concerned, and especially with the question of peripheral resistance.

Planned Hypotension.

The idea of planned hypotension to reduce surgical haemorrhage was introduced by Griffiths and Gillies in 1948, when they achieved it using the total spinal technique for thoraco-lumbar splanchnicectomy and sympathectomy. In a stimulating paper, they maintain that hypotension is of serious import only when the causative mechanism is haematogenic and is relatively innocuous when of neurogenic origin, the important differential factor being the state of the capillary bed; further, in acute total sympathectomy, the reduction in peripheral arteriolar resistance enables a pressure slightly in excess of 30 mm. Hg (which represents the sum of the venous pressure and the colloid osmotic pressure of the plasma) to maintain an adequate capillary circulation—in the presence of a normal blood volume and capillary tone.

The major part of the peripheral resistance is situated in the arteriolar bed (Best and Taylor, 1945). If this is removed by arteriolar vaso-dilatation it is evident that a relatively low head of pressure (e.g., 60 mm. Hg) will suffice to drive blood through into the capillary bed where the normal pressure is less than 30 mm. Hg and where oxygen/carbon dioxide exchange and tissue respiration occur.

Pharmacological Sympathectomy.

Subsequently, Enderby (1950) achieved this acute total sympathectomy by pharmacological means using pentamethonium iodide (C5), which paralysed the autonomic ganglia, thus abolishing vaso-motor tone.

It was realized early that *posture* was an important factor in bringing about the desired fall in blood pressure. This " controlled circulation " can thus bring about a *postural ischaemia*, which finds an obvious field of application in operations on the head and neck. In a later paper (Enderby and Pelmore, 1951) improved results were described using hexamethonium bromide (C6).

The Methonium Compounds.

The pharmacology of the methonium compounds has been extensively studied by Paton and Zaimis (1948, 1949, 1951)

and others. These methonium compounds are polymethylene bistrimethylammonium salts with the formula $[(CH_3)_3\ N^+(CH_2)_n\ N^+(CH_3)_3]\ 2Br$ or I, where n = 6 for hexa- and 5 for pentamethonium.

Two of them (pentamethonium and hexamethonium) act on the autonomic nervous system as specific ganglionic blocking agents, by interfering with the transmission process at the ganglionic synapse itself. This interference is produced by the mechanism of "receptor competition"—i.e. they compete successfully with acetylcholine (the release of which is not interfered with) for receptor groups on the ganglion cell membrane. Their action is thus analogous to that of curare at the motor end-plate of the myoneural junctions in the somatic nervous system.

On the sympathetic side of the autonomic nervous system their chief effect is, of course, to produce a hypotension, the degree of which depends on several factors:

(1) *Initial level of blood pressure.* The fall in systolic blood pressure appears to bear a direct relationship to its initial level. It is suggested that the resting sympathetic tonus is subject to considerable individual variation.

(2) *Posture.* The relaxation of venomotor tone is possibly a factor of importance in producing the dry field (Paton, 1951). Gravity is brought into play to assist the venous return from the site of operation to the heart.

(3) *Choice of Drug.* The concensus of opinion indicates that hexamethonium is rather more powerful and certain in its action than pentamethonium—although Barnett (1951) disagrees. Paton and Zaimis (1951) state that the relative potencies of the two drugs (in the rabbit) are as follows:

		C5	C6
(*a*)	on superior cervical ganglion	80	100
(*b*)	on peristaltic reflex of ileum	33	100
	$(a)/(b)$ =	2.4	1

It is thus evident that the "spectrum of ganglionic sensitivity" varies with each drug; while C5 is only four-fifths as effective as C6 in paralysing the sympathetic ganglia, what is more important is the fact that C5 is only one-third as effective as C6 in paralysing the *parasympathetic* ganglia. Further, it will be seen that C6 exerts an equal effect on all autonomic ganglia, whereas C5 is about $2\frac{1}{2}$ times more effective on sympathetic than on parasympathetic ganglia. This, in my opinion, makes C5 the drug of choice for controlled hypotension, and is an important point in the avoidance of "side-effects" due to paralysis of the parasympathetic ganglia—for example, in the bowel and bladder.

(4) *Dosage.* There is an optimal dosage which will paralyse the ganglia, and to exceed this will not produce any greater fall in blood pressure—although the fall may be more prolonged (Enderby, 1950).

It would appear from the present series of cases that the best results are obtained by using a large initial dose of pentamethonium (up to 100 mg.) followed, if required, by a supplementary dose of hexamethonium (up to 50 mg.). It is un-

necessary and unprofitable to exceed this dosage.

Their specificity of action and freedom from true side effects (i.e. actions other than ganglionic blockade) has rendered these drugs of value in anaesthesia.

PRESENT SERIES

The present series of cases consists of twenty fenestrations which although only a small number represents over eighty hours anaesthetic time.

The patient is usually a fit young woman, more often blonde (Cawthorne, 1952). The average age was 34 years, the youngest being 19 years and the oldest 46 years.

The pre-operative examination included a haemoglobin estimation and, in most cases, an electrocardiogram.

Premedication consisted of papaveretum 1/3 grain (20 mg.) and hyoscine 1/150 grain (0.45 mg.).

Anaesthetic Technique.

The patient is placed on the operating table and the pulse and blood pressure taken. Anaesthesia is induced with thiopentone 500–750 mg. followed by a relaxant, usually gallamine (Flaxedil) 60–80 mg., to facilitate intubation. The lungs are inflated with oxygen, the cords sprayed with 2 per cent amethocaine, and a No. 10 or 11 oral endotracheal tube lubricated with 2 per cent cinchocaine is passed. This is connected with a No. 4 Magill's T-piece to the Boyle's apparatus and anaesthesia maintained with nitrous oxide (7 l.) and oxygen (3 l.) with intermittent thiopentone as required.

The blood pressure is again taken and the patient, strapped to the table, is postured in the 30° reverse Trendelenburg position, the head being held steady by a head-band. On taking a further blood pressure reading it is usual to find a fall, although the systolic pressure is not as a rule below 100 mm. Hg.

RESULTS

The posture used is illustrated in figures 1 and 2, while table I summarizes the results obtained. The average dose of thiopentone was 1200 mg. The average dose of hypotensive drug (calculated as C5 and excluding procaine amide) was 128 mg.; this maintained the systolic blood pressure below 80 mm. Hg for an average time of about one hour. The "result" indicates the state of the operative field as assessed by the surgeon. This is not always directly related to the level of the blood pressure.

DISCUSSION OF CASES

Cases 1 and 2 were given a slow intravenous drip of normal saline as a vehicle for injections, but this was found to be both unnecessary and undesirable. In these cases, also, hypotension was induced as soon as the patient was postured and maintained at a systolic blood pressure of 60–80 mm. Hg for three hours throughout almost the entire procedure. Although these patients showed no ill effects it was considered unnecessary to maintain the hypotension for so long. Accordingly, in subsequent cases bleeding from skin and soft tissues was controlled by prior injection of 1 per cent lignocaine and adrenaline 1/100,000 and by the use of the diathermy; bleeding from bone during the mastoidectomy was controlled by posture and thiopentone; while pentamethonium

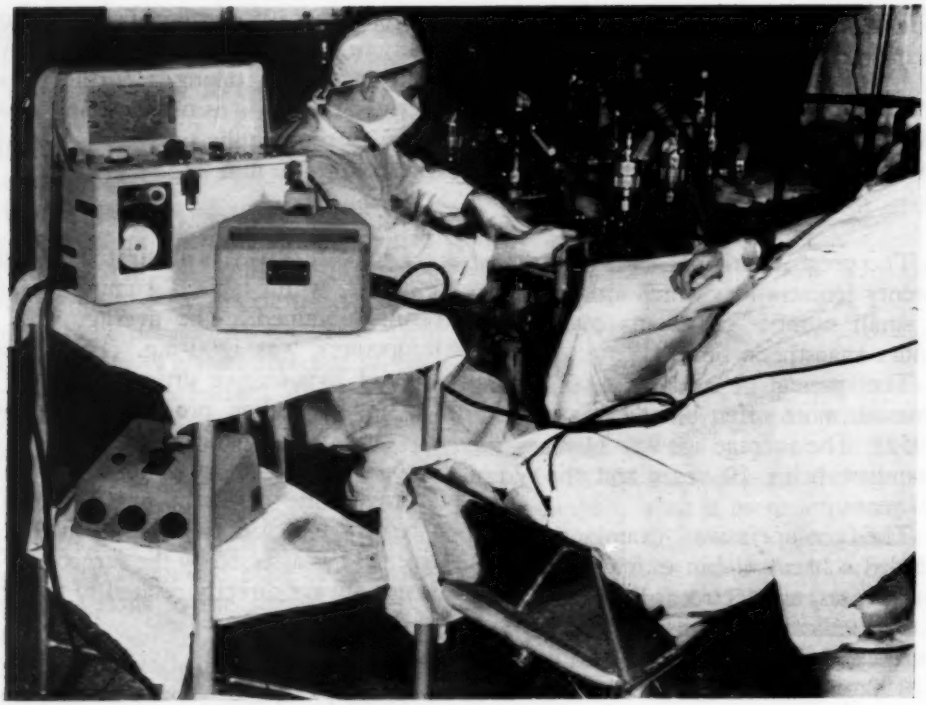

FIG. 1

The steep foot-down tilt of the table is clearly seen. The patient is held in position by a foot-rest and knee-strap; an arm is easily accessible for injections. The leads go to the electrocardiograph on the table at the left. In front of this is the oximeter, with its transformer below.

was reserved to control bleeding from bone during the actual fenestration, a procedure occupying rather less than an hour.

Case 3 (fig. 3) illustrates a point concerning the choice of relaxant. It might be thought rational, when using pentamethonium in any event, to use decamethonium (C10) as a relaxant for intubation. This case in fact received decamethonium 4 mg. without showing marked respiratory depression, but the subsequent course of hypotension was unsatisfactory in that, even with a dosage of pentamethonium as high as 300 mg. and a steep tilt (40°) on the table, it was possible to lower the systolic blood pressure below 80 mm. Hg only for a short time. There seems to be a possibility of antagonism between these two drugs, although Davison (1951) states that he has not noticed this.

Suxamethonium chloride (Scoline) was used in three cases, but it was found that its very brevity of effect necessitated the early introduction of trichlorethylene to prevent the patient straining on her endotracheal tube. The use of trichlorethylene was clearly undesirable when electro-

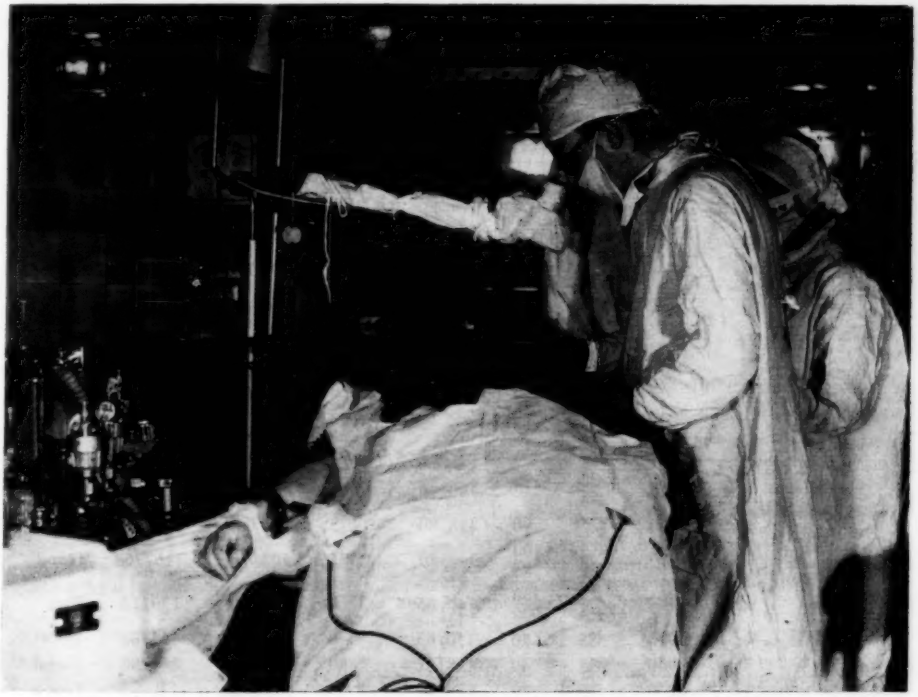

FIG. 2
Shows the surgeon examining the completed fenestra through his microscope.

cardiograms were being taken. Accordingly, reversion was made to the use of a modest dose of gallamine, respiration being assisted as required. No increase in bleeding was noticed.

A dry operative field cannot, of course, be achieved without meticulous attention to the patency of the airway and the efficient excretion of carbon dioxide. Thus, in two cases in which there was a fair amount of oozing, slight improvement was obtained (after a time) by the use of an open T-piece arrangement as described by Bullough (1952).

A point concerning the choice of hypotensive drug is illustrated by Case 8 (fig. 4). Although hexamethonium is rather more powerful and certain in its action than pentamethonium, nevertheless, as already stated, the latter is preferred. However, it may be extremely difficult to *maintain* a satisfactory degree of hypotension with this drug, especially in a fit young man. In this case pentamethonium 90 mg. produced a satisfactory fall in systolic blood pressure from 150 mm. Hg to 55 mm. Hg, but it soon started to rise, and in 20 minutes was 70 mm. Hg. As a further gradual rise in blood pressure was anticipated, and the fenestra was not yet near completion, a test dose of 100 mg. of procaine amide

TABLE I

Anaesthesia with hypotension for fenestration Synopsis of results.

Case No.	Age in years	Duration in hours	Dosage of Thiopentone in mg.	Hypotensive in mg.		Blood pressure in mm. Hg Pre-op.	S.B.P. <80 for (min.)	Table level post-op.	After four hours	Result
1	40	4	1300	C5	160	210/110	180	90/50	150/75	Good
2	42	4	1500	C5	120	130/80	160	85/45	104/76	Good
3	35	4½	1400	C10 C5	4 300	136/102	30	100/50	135/90	Fair
4	42	4½	1800	C5 C6	90 50	116/62	40	100/55	120/60	Good
5	45	4½	1800	C5 C6	100 100	135/75	15	95/60	128/68	Good
6	46	5	2000	C5	50	160/90	120	110/60	120/80	Fair
7	19	4½	1500	C5 C6 PA	90 90 900	150/90	25	110/60	130/85	Fair
8	41	4½	1750	C5 PA	90 1000	140/90	90	90/50	110/75	Good
9	22	3½	900	C5	90	118/80	75	100/60	130/80	Good
10	33	4½	1200	C5 C6	100 45	140/80	75	102/76	116/76	Good
11	40	4½	800	C5 PA	100 1000	140/65	0	105/70	130/75	Fair
12	25	4	1000	C5	50	150/85	0	130/75	145/80	Poor
13	46	3½	1000	C5	40	138/82	80	110/65	140/80	Good
14	21	4	1250	C5	100	135/80	55	100/60	130/75	Good
15	31	4	1500	C5 C6 PA	100 50 900	110/65	75	80/50	100/70	Good
16	19	3½	600	C5	100	130/85	45	100/60	112/80	Good
17	40	4	600	C5	100	125/70	60	100/50	115/75	Good
18	27	4½	800	C5 C6 PA	100 50 1000	130/80	0	100/70	130/70	Fair
19	31	3½	1000	C5	100	120/84	0	105/60	115/80	Fair
20	40	3	800	C5	100	140/80	65	95/55	140/75	Good
Average	34	4.2	1200	C5	128		59			

(Pronestyl) was given. This was followed by doses of 600 mg. and 300 mg. As a result of this, the systolic blood pressure fell again to 55 mm. Hg and remained below 70 mm. Hg for a further half-hour, thus allowing the fenestra to be completed in a bloodless field.

It appears that procaine amide potentiates the hypotensive action of the methonium drugs in two ways (Mason and Pelmore, 1953): (1) by an additive vasodilatory effect, and (2) by increasing the refractory period of the heart muscle, thus preventing the compensatory tachycardia which often follows pentamethonium and tends to maintain the cardiac output.

Not in all young people, however, is

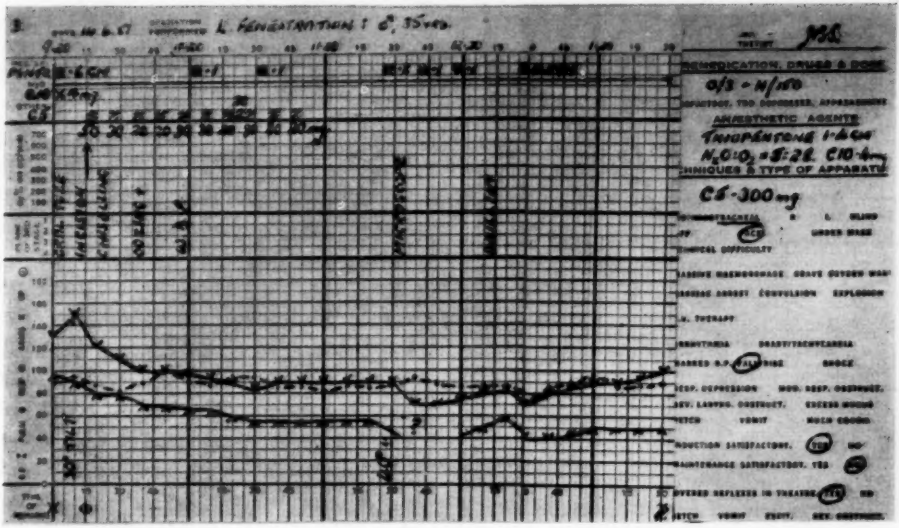

FIG. 3

Case 3 had 4 mg. C10 (for intubation) and 300 mg. C5 (in divided doses). There was considerable difficulty in producing a satisfactory degree of hypotension, but the operative field was fair and the functional result good.

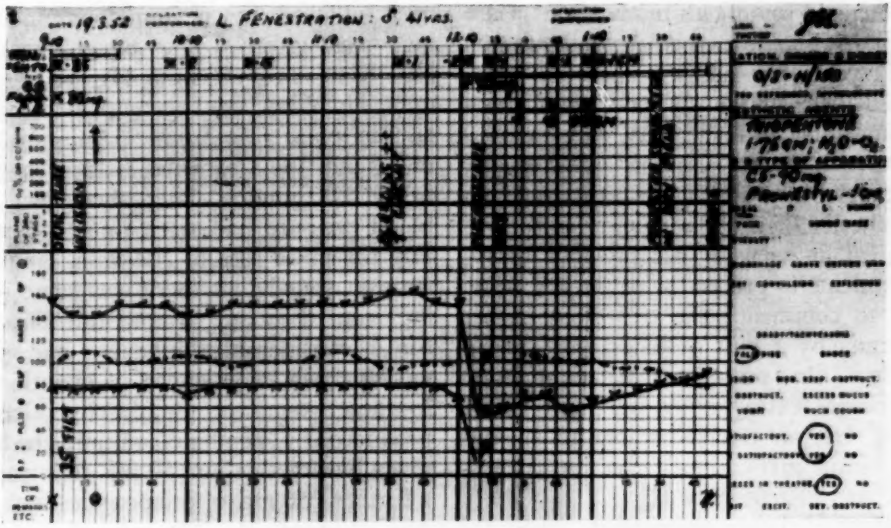

FIG. 4

Case 8 shows the effect of procaine amide in maintaining the hypotension produced by pentamethonium

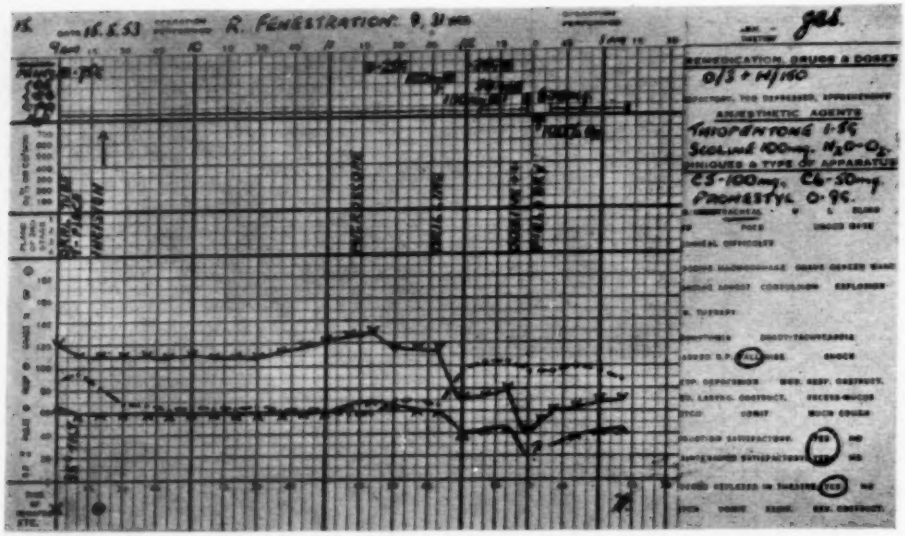

FIG. 5

Case 15 was a young woman of 31 years with Hb 65 per cent. She showed a rather excessive fall in blood pressure (S.B.P. 40 mm. Hg) after the potentiation of 100 mg. C5 by 50 mg. C6 and 900 mg. procaine amide.

hypotension so difficult to maintain. Case 15 (fig. 5) illustrates this. A young woman of 31 years had had the operation postponed twice previously, once on account of anaemia, and she was very anxious to have it done. On this occasion her haemoglobin was 65 per cent and red blood cells 3.5 million/cu.mm., but it was decided, in view of her previous disappointments to proceed with the operation and to commence the treatment of her anaemia by a pint of blood post-operatively. On pre-operative examination occasional extrasystoles were felt at the wrist, but an electrocardiogram showed only sinus arrhythmia. Her blood pressure was 110/65 mm. Hg.

After $2\frac{3}{4}$ hours anaesthesia, when the surgeon was about to commence drilling out the fenestra, thiopentone 250 mg. followed by pentamethonium 100 mg. was given. The blood pressure fell from 114/60 mm. Hg to 70/40 mm. Hg; this was accompanied by a rise in pulse rate from 56/min to 96/min., but the operative field was dry. Some 20 minutes later, however, the blood pressure had risen to 80/45 mm. Hg, the pulse rate to 104/min., and the surgeon stated that there was some oozing from the bone around the fenestra. Since considerable difficulty had previously been experienced in maintaining in these young people the hypotension produced by pentamethonium, she was given hexamethonium 50 mg. followed by a further 250 mg. of thiopentone, and this was followed by 800 mg. of procaine amide (of which a test dose of 100 mg. had previously been given).

As a result of this rather intensive therapy the systolic blood pressure fell to 40 mm. Hg. This was the more disturbing since there was still marked respiratory depression due to the recent dose of thiopentone. Respiration was, of course, being assisted at this point, using 100 per cent oxygen. Operating conditions were now ideal! The tilt of the table was about to be reduced when a further reading showed the systolic blood pressure to be 50 mm. Hg: respiration was now almost adequate. Shortly thereafter the systolic blood pressure rose to 60 mm. Hg and adequate spontaneous respiration was resumed. Nitrous oxide was then reintroduced. The patient's colour was satisfactory throughout. On levelling the table at the conclusion of the operation, the blood pressure rose to 80/50 mm. Hg. Recovery was uneventful.

In retrospect, it may well be that one factor which contributed to the somewhat precipitous fall in blood pressure was the moderate degree of anaemia. This would result in a decrease in the viscosity of the blood, and consequently in the peripheral resistance. Further, the hypotensive effect of the rather liberal supplementary dose of thiopentone would no doubt be aggravated by that circumstance.

IMMEDIATE POST-OPERATIVE MANAGEMENT

When the skin is closed the table is levelled and the systolic blood pressure, which as this stage is usually about 70–80 mm. Hg, now rises to about 90–100 mm. Hg. On withdrawal of anaesthesia, the patient's cough reflex is present; her pupils are, of course, large. Recovery from anaesthesia is not delayed and the patient is moving or even talking when the bandaging is complete. She is sent back to the ward with the sphygmomanometer cuff still in position and 2-hourly blood pressure readings are taken. She is kept flat for 4 hours at the end of which time the systolic blood pressure is found to be over 100 mm. Hg, although usually still below its normal level.

It is considered desirable to allow the blood pressure to rise gradually to its normal level during the afternoon. The use of vasopressor drugs is both unnecessary and unwise, and this may interfere with the natural processes of clotting and promote reactionary haemorrhage.

Post-operative sedation is assured by morphine $\frac{1}{4}$ grain (16 mg.) while nausea and vertigo of labyrinthine origin are controlled by promethazine 8-chlorotheophyllinate (Avomine) 25 mg.

POST-OPERATIVE COURSE AND COMPLICATIONS

Case 3, which had been rather unsatisfactory all through, since his blood pressure did not fall low enough, showed a fair amount of post-operative staining, and developed a haematoma of his wound which subsequently required evacuation. However, his functional result showed a good and sustained improvement in hearing.

There were two cases of urinary retention. Case 8, having passed 6 oz. (170 ml.) of urine in the evening, had some difficulty with micturition the following day; he was given 1 ml. (0.25 mg.) of Carbachol, passed 10 oz. (284 ml.) of urine, and had no further trouble. Case 16, a nervous young girl, also complained of difficulty

with micturition, and was catheterized twice.

As a result of the labyrinthine irritation, nausea and dizziness were frequent in the first 48 hours and vomiting and nystagmus sometimes occurred. The pupils usually remained dilated for several hours due to paralysis of the ciliary ganglion, but in no case was this present the next day. Dryness of the mouth was a not infrequent complaint, possibly due to paralysis of the secreto-motor fibres from the submandibular ganglion; a simpler explanation, however, would be the by-passing of the normal respiratory passages by the endotracheal tube.

RISKS OF HYPOTENSION

No article on hypotension would be complete without some reference to the possible hazards involved.

In an indictment of hypotension, Davison (1953) talks of "the frequency of difficulty in reversing the hypotensive action of methonium" and states that "this commonly requires the administration of a vaso-pressor." Mandow *et al.* (1954), using a very liberal dosage, concur. This has certainly not been my experience, confined as it has been to cases in which blood loss was not a factor. Although methyl-amphetamine (Methedrine) is always at hand, it has never been required; on the contrary, the chief difficulty has been to get the pressure down.

Electrocardiographic Evidence.

In a consideration of anaesthesia for the cardiac patient Hayward (1952), while pointing out that severe coronary artery disease may be symptomless, states: "provided the coronary arterial system is healthy, it is unlikely that coronary insufficiency will appear if hypotension is produced by ganglion blocking drugs as, in spite of a decreased coronary blood flow, the work of the heart and the metabolic needs of the cardiac muscle are reduced in proportion." This is in direct contrast to the existing state of affairs when hypotension is produced by arteriotomy with concomitant vasoconstriction (Harris and Hale, 1947).

In order to ascertain whether there was any interference with the nutrition of the heart during the hypotensive period, electrocardiographic records were taken in several patients. As it was impracticable to apply chest leads in theatre, the classical limb leads were employed.

The results obtained in Case 17, a woman of 40 years, are typical: no change occurred in the electrocardiograms after 100 mg. of pentamethonium, although the blood pressure fell to 65/45 mm. Hg and the systolic blood pressure was maintained below 80 mm. Hg for an hour. The report read as follows: "No electrocardiographic abnormalities have been demonstrated in these patients. Cardiac upset might, however, be shown in older patients after long periods of hypotension, or where procaine amide was used as a hypotensive agent."

Thus the evidence, so far as it goes, does not indicate any interference with the coronary circulation.

Oximetric Evidence.

Some concern has been expressed for the adequacy of the cerebral circulation during the hypotensive phase. Morris *et al.* (1953) found "a significant decrease in cerebral blood flow following marked

depression in the mean blood pressure in spite of a decrease in cerebral vascular resistance. Cerebral oxygen consumption was only slightly decreased due to a more complete extraction of oxygen from the blood flowing through the brain." On the other hand, Hampton and Little (1953) quote Stone, who found the cerebral blood flow in young adults unchanged following a reduction in mean arterial pressure of 40–50 per cent by hexamethonium. Regarding the present small series of cases, the normal character of the respiration, the immediate recovery from anaesthesia, and the absence of any post-operative complications are clinical grounds for assuming that the cerebral circulation was unimpaired.

It has recently been possible, however, to carry out oximetry in four patients. The object of this has been to determine the percentage of oxygen saturation of the arterial blood of the forehead (and, by inference, of the brain) while the patient is in the reverse Trendelenburg position during the hypotensive state.

Principles and Method. A small area of the skin of the forehead is first histaminized by iontophoresis, for 3–5 minutes at a current of 1–2 mA, of an 0.6 per cent aqueous solution of histamine phosphate. The object of this is to produce a constant, maximum and rapid circulation therein, and enable arteriolar (rather than capillary) saturation to be measured by the cyclops, a photo-electric cell with red and green filters, which is placed over the spot. The method is based on the measurement of the intensity of light reflected by the blood: red light (600–680 mμ) is strongly reflected by oxyhaemoglobin, and in this wavelength the logarithm of the reflected quantity of light is a linear function of the oxygen saturation (Zijlstra, 1951).

Results. In no case was there any significant alteration in the percentage oxygen saturation of the arterial blood of the forehead during the hypotensive phase, although the patient was in the reverse Trendelenburg position. This would tend to support the clinical evidence that the cerebral circulation is unimpaired during hypotension. In coming to this conclusion, it should be stressed that these patients are young fit adults with healthy elastic cardiovascular systems.

CONCLUSION

It would appear that planned hypotension using pentamethonium iodide is a safe procedure in fit adults undergoing fenestration of the labyrinth. Further, it produces the bloodless field which is not merely a help in the technical performance of this operation but is an essential to its ultimate success.

SUMMARY

The anaesthetic requirements for the fenestration operation are discussed. These lead to a consideration of the physiological factors influencing surgical haemorrhage, and the modification thereof, using planned hypotension achieved by the pharmacological sympathectomy produced by the methonium drugs. The anaesthetic technique used in a small series of fenestrations is then described, and the cases discussed in some detail, including their immediate post-operative management, subsequent post-operative course and complications. The risks of induced hypotension are finally con-

sidered, and some electrocardiographic and oximetric evidence is presented in support of the conclusion.

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INDUCED HYPOTHERMIA AS A THERAPEUTIC MEASURE IN NEUROLOGY

A Clinical Study of a "Hopeless" Case

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ALTHOUGH hypothermia has only recently been introduced as a therapeutic agent in surgery and anaesthesia, it is already proving of value because of the reduction in tissue oxygen consumption that occurs when the temperature is lowered (Bigelow, Lindsay, Harrison, Gordon and Greenwood, 1950). Recent reports concern its application to cardiac surgery (Lewis and Tuffic, 1953; Swan, Zeavin, Blount and Virtue, 1953) and to general surgery for poor risk cases (Dundee, Gray, Mesham and Scott, 1953; Dundee and Mesham, 1954). Its application in acute head injuries with mid-brain lesions has been reported by Woringer, Schneider, Baumgarter and Thomalske (1954).

In a previous communication we have drawn attention to the value of combining hypothermia with hypotension during major neurosurgical operations (Dundee, Francis and Sedzimir, 1954). The present report deals with a neurosurgical case in which hypothermia was employed, first to increase the safety of hypotension at operation, and later, on two occasions, as a therapeutic measure. The patient survived for twenty-eight days following a massive intracerebral haemorrhage from a saccular aneurysm which was operated upon during the bleeding phase. The artificial reduction in cerebral metabolism is thought to be the main factor responsible for the prolonged survival and the astonishing preservation of function in areas of brain devoid of their main blood supply.

The method of producing hypothermia will not be discussed in detail, but surface cooling was used throughout. Chlorpromazine and hexamethonium were given to produce peripheral vasodilatation. Shivering was prevented by analgesic drugs (pethidine and levorphan) and chlorpromazine (Dundee, Mesham and Scott, 1954).

CASE REPORT

Mrs. S., aged 40, was admitted to a medical ward on 17.3.54. Two and a half hours before admission, while polishing furniture, she was struck by a severe headache and became unconscious. She vomited on regaining consciousness and complained of severe diffuse headache.

On examination, she was found to be drowsy and restless but was able to co-operate for the simpler

tests. Neck rigidity was present. Apart from the optic fundi which were not examined, all the cranial nerves were normal. Motor power, sensation and reflexes were also normal. There was no abnormality in the respiratory, cardiovascular or alimentary systems. Blood pressure was 130/80, pulse 86 per minute and of normal rhythm. A lumbar puncture revealed heavily blood-stained fluid under a pressure of 350 mm. water. On 19.3.54 a full neurological examination revealed no abnormality except for an equivocal right plantar response. Her mental faculties were fully preserved. On 23.3.54 she had another, but less severe, subarachnoid haemorrhage without any localizing signs.

Angiography (25.3.54, C.B.S.)

Under light anaesthesia, percutaneous angiography was performed on the right carotid artery, taking lateral and axial views. During the injection for axial exposures, the opposite carotid artery was compressed in order to ascertain the collateral circulation. The lateral views showed an aneurysm on the middle cerebral artery measuring 10 × 4 mm. and projecting downwards. The supraclinoid segment of the internal carotid artery was in spasm and there was a generalized spasm of the middle cerebral tree. The posterior cerebral artery was filled, but the anterior cerebral artery did not show. The axial views placed the aneurysm 1.5 cm. from the usual position of bifurcation of the internal carotid artery. The anterior cerebral artery was again absent despite the compression. Under such circumstances it is our routine to perform bilateral angiography at once, but for technical reasons left-sided angiography was postponed.

The patient was examined later the same day. She was none the worse for the investigation and declared that the headache was less severe. Four days later, at 8.45 a.m., she suddenly lost consciousness for fifteen minutes. She was incontinent but there were no convulsions. When she came round she was very restless and complained of severe occipital headache. At 11 a.m. she did not respond to verbal commands. Her pupils were small and did not react to light. The fundi were normal. There was a supranuclear paresis of the left side of the face, and a gross weakness of the left arm. The left leg was not paralysed but there was patellar and ankle clonus. Bilateral extensor plantar responses were present. The neck was not stiff at that time, but the rigidity became marked within the next hour.

On 3.4.54 she was comatose, responding only weakly to painful stimuli. Her breathing was rapid, shallow and irregular. Her temperature rose to 102°F, her pulse rate remaining between 112 and 120 per minute. Her temperature was kept at the 99° level by frequent sponging, and in the evening she responded slowly to verbal commands. There was a further improvement the following day and operation was decided upon.

On the morning of 5.4.54, as she was leaving the ward, she spoke a few words to the Ward Sister. On arrival at the theatre she was in deep coma. The right pupil was dilated and did not react to light. There was a complete left hemiplegia, and it was evident that she was bleeding intracerebrally. It was decided to proceed with the operation in view of the apparently hopeless prognosis.

Anaesthetic notes (J.W.D.)

Premedication was with chlorpromazine 50 mg. and hyoscine 1/150 grain (0.42 mg.). Anaesthesia was induced with 100 mg. thiopentone and 20 mg. suxamethonium. An armoured endotracheal tube was passed, the pharynx packed with moist gauze and the anaesthesia was continued with nitrous oxide-oxygen by a T-piece technique.

Details of anaesthetic and operation are shown in figure 1, her immediate pre-operative condition being indicated at A.

First operation (C.B.S. and D.J.)

Right fronto-temporal craniotomy. On opening the dura the whole area of exposed brain showed deep blood-staining. The brain itself was extremely friable. The Sylvian fissure was opened and immediately intracerebral blood clot was encountered. As soon as suction was applied to the clot, fresh arterial bleeding ensued. The aneurysm was then quickly exposed by further suction and the moderate haemorrhage was controlled by gently nipping the aneurysm with dissecting forceps. More of the surrounding blood clot was removed and it was then seen that the main trunk of the middle cerebral artery divided into three branches, a sessile aneurysm sitting astride two of them, while the third emerged from the sac itself. An attempt at clipping off the base of the aneurysm was unsuccessful and a clip was applied to the stem of the artery just proximal to the sac. The bleeding ceased instantly (B, fig. 1). When all the intracerebral clot was removed, it was evident that the anterior two-thirds of the temporal lobe had been destroyed and that the adjoining areas of the frontal and parietal lobes were also involved. Posteriorly the clot filled the temporal horn as far as the trigone. During further haemostasis a pint of blood was given quickly (C, fig. 1), thus raising the blood pressure to 85 systolic. The dura was then sutured and the wound closed in the usual manner (D, fig. 1).

Post-operative progress.

Within 30 minutes of the conclusion of the operation (E, fig. 1) the patient responded to minor painful stimuli by groans and purposeful movements of the right limbs and the left lower limb. There was an appreciable movement of the left shoulder, but no more distal movements were seen in that arm. At 11 p.m. her rectal temperature was 97°F. She responded instantly to any minor stimuli by groaning, opening her eyes and moving her limbs. The power of the left leg was as good as that of the right, but surprisingly there was now movement of the left shoulder, elbow, wrist and fingers. These movements were of good range against gravity and at the elbow there was power against resistance. Noxious stimuli over the left side of the body were localized fairly accurately. The pupils were equal and reacted to light.

During the second half of the night her condition deteriorated. At 10 a.m. on 6.4.54 she showed very little response to painful stimuli, and the right pupil was dilated and fixed. There was no movement of her left limbs. Her temperature had risen and cardiac and respiratory rates were very rapid. It was decided to re-explore the wound to exclude compression by a blood clot.

Second operation (C.B.S.)

The flap was re-elevated. The brain was extremely tense and swollen and was oozing between the dural sutures. The depths of the Sylvian fissure were inspected and there was no evidence to clot. A right frontal lobectomy was performed in order to provide internal decompression for the massive oedema of the hemisphere. The dura was left unsutured, the bone flap was allowed to ride freely.

8 p.m. Despite frequent sponging, tachycardia, tachypnoea and hyperthermia persisted and there was no neurological improvement.

Second hypothermia.

7.4.54 (fig. 2). This was commenced at 12.45 a.m. and continued until 10 a.m. At the onset (*a*) her right pupil was dilated and fixed and the left hemiplegia complete. Approximately one hour later (*b*) the pupil became smaller and showed a slight reaction to light. She became more active generally and began to move the left leg freely although the paresis was marked. When her temperature was reduced to normal (*c*) some movements of the left shoulder and elbow were noticed and her conscious level was slowly but noticeably rising. Although the drugs and ice were discontinued at 10 a.m., she remained uncovered and the improvement reached at this time was maintained for the following thirty-six hours.

10.4.54. Temperature, pulse and respirations started to rise in the evening. A complete right third nerve palsy developed.

11.4.54. Her condition began to deteriorate seriously in the afternoon. Both pupils became dilated and fixed; there was no movement in the left arm and very little movement in the left leg. Her general response to stimulation was very feeble.

Third hypothermia.

5 p.m., 11.4.54. (fig. 3). Three hours after the commencement her pupils became smaller, showing a little reaction to light, and responsiveness was increasing (A).

On 13.4.54, exactly forty-eight hours after the start (B), the following examination was recorded: " She now opens her eyes whenever touched and occasionally follows the examiner with her gaze. There is a partial recovery in the third nerve palsy. Both pupils are of medium size and react to light. She moves her right limbs and left lower limb purposefully and slight movement has returned to her left shoulder and elbow. She shows a delayed response to painful stimuli applied to the left side of her body."

General management.

Throughout the whole period of hypothermia, in addition to half-hourly temperature, pulse and respiration observations, the patient was attended two-hourly for the purpose of turning, feeding, etc. Water glucose-saline, milk and Casilan were given in rotation by Ryles tube, supplemented with vitamins and potassium. Naso-pharyngeal and tracheal secretions were aspirated whenever necessary. Penicillin and streptomycin were given parenterally.

At 9.30 p.m. on 14.4.54 her temperature again reached 98°F for the first time since the onset of this cooling. For the next two days her temperature remained between 98°F and 99.5°F, her skin temperature between 86°F and 97°F, her respiration between 20 and 24 per minute, and her pulse between 110 and 130 per minute. There was a steady improvement in her general condition.

Subsequent course.

17.4.54. Weak movements of her left fingers were again observed.

19.4.54. She began to respond to verbal commands. She would open her eyes on request and squeeze the examiner's hand. On stimulation movements of the left shoulder, elbow and fingers became more marked. Tonus which had so far fluctuated between flaccidity and slight resistance, became definitely increased. Reflexes were all brisk, the right more so than the left, although the right plantar response was flexor compared with a definite left extensor. She did not utter a word and would not take anything by mouth apart from a few sips of water.

22.4.54. Lumbar puncture: pressure 150 mm.; clear colourless fluid containing 6 lymphocytes per c.mm. and a protein of 120 mg. per cent. Blood: white cells 16,000 per c.mm.; serum chlorides 680 mg. per cent; potassium 19.5 mg. per cent; sodium 360 mg. per cent.

28.4.54. X-ray chest: normal.

30.4.54. Both her husband and the House Surgeon, on separate occasions, reported that she had nodded her head when asked if she recognized the husband. She again looked to be on the point of speaking. For most of the day she sat in an easy chair propped up with pillows, staring expressionlessly to the front or dropping off to sleep. Her mask-like facies only altered when attention was paid to her and then her expression changed to one of apparent displeasure at being disturbed, accompanied by an occasional groan or a slight grimace. The right ptosis was slight but there were grossly defective inward, upward and downward movements of this eye. The right pupil was circular and of medium size but there was no reaction to light. The optic fundi were normal. The power of the left leg was poorer than previously and movements of the left fingers were again absent, but apart from these there was no alteration in the findings recorded on 19.4.54.

2.5.54, 2.15 a.m. She had a fit of coughing witnessed by a nurse and died instantly. Her death was thought to be due to pulmonary embolism.

Post-mortem examination.

3.5.54. The thoracic and abdominal organs were normal.

Brain. The right cerebral hemisphere was soft and " mushy " throughout, including the occipital lobe and the region of the basal ganglia. The left hemisphere and the cerebellum appeared macroscopically normal, as did the brain stem. The right middle cerebral artery was completely occluded by a clip applied proximally to a shrivelled saccular aneurysm. Another clip was *in situ* on a small branch emerging from the aneurysm. Other cerebral vessels and both internal carotid arteries appeared to be normal.

DISCUSSION

Within a period of fifteen days, this patient suffered from five incidents of

haemorrhage from an aneurysm on the right middle cerebral artery. The first two were purely subarachnoid, the third had a minor cerebral component, and the fourth resulted in a profound cerebral lesion. On the day of operation, during transport to the theatre, a massive intracerebral haemorrhage occurred

The operation was undertaken on a comatose patient with a dilated and non-reacting pupil, a left hemiplegia and concurrent hyperthermia, hyperpnoea and tachycardia (A, fig. 1). Clinically this was the syndrome of gross interference with mid-brain function, the gravity of which is well known. The aneurysm was still bleeding when exposed, although the blood pressure had been lowered artificially (B, fig. 1). The technical performance of the operation was greatly facilitated by the hypotension produced by Arfonad. In the light of subsequent events such a degree of hypotension was probably only made safe by the concurrent use of hypothermia.

During operation the following facts were established and are stressed in relation to the post-operative clinical findings:

(1) Clipping of the middle cerebral artery 1 cm. from its origin, thus

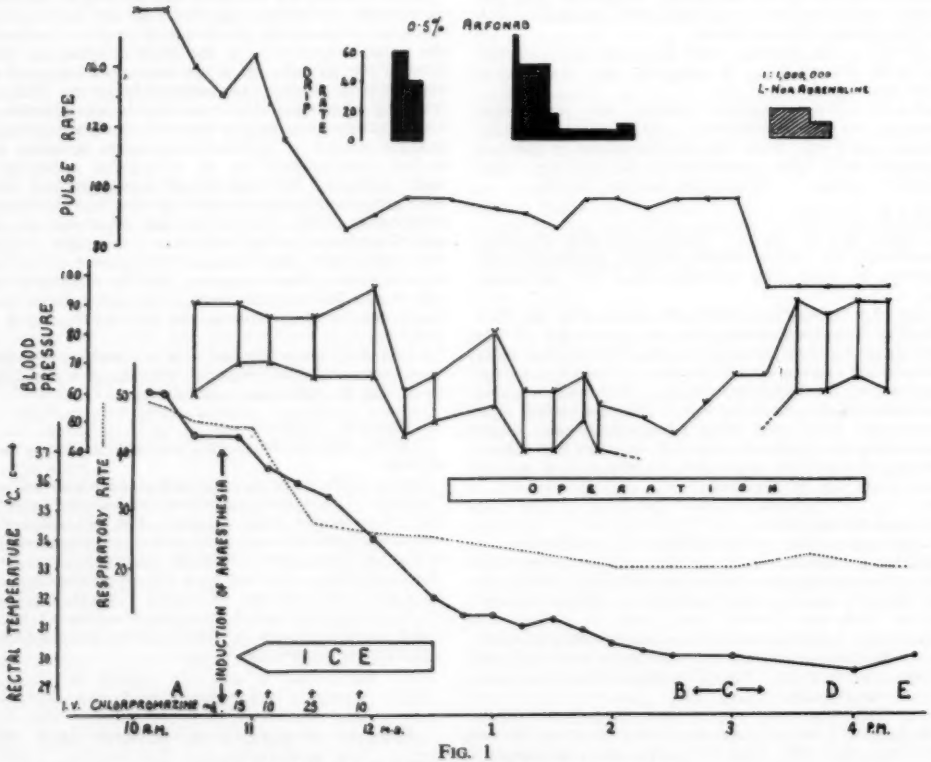

FIG. 1

Details of the first hypothermia and operation.

cutting off the main blood supply to the whole territory of its distribution.

(2) About two-thirds of the right temporal lobe was destroyed by the massive intracerebral haemorrhage, and the adjoining areas of the parietal and frontal lobes were damaged.

Despite the gravity of the pre-operative condition and the profound lesion sustained by the right hemisphere the patient rapidly began to regain consciousness. Activity in the left limbs was apparent within thirty minutes (E, fig. 1). During the next few hours, while her temperature was still just below normal, she responded instantly to minor stimuli and had a normal power in the left lower limb. There was a good movement against gravity in the left upper limb, including the wrist and fingers, and elbow flexion was present against resistance. There was fairly accurate localization of stimuli applied to the left side of the body. The right pupil became normal in size and reacted to light. Over the following twelve hours her temperature, respirations and pulse rates rose

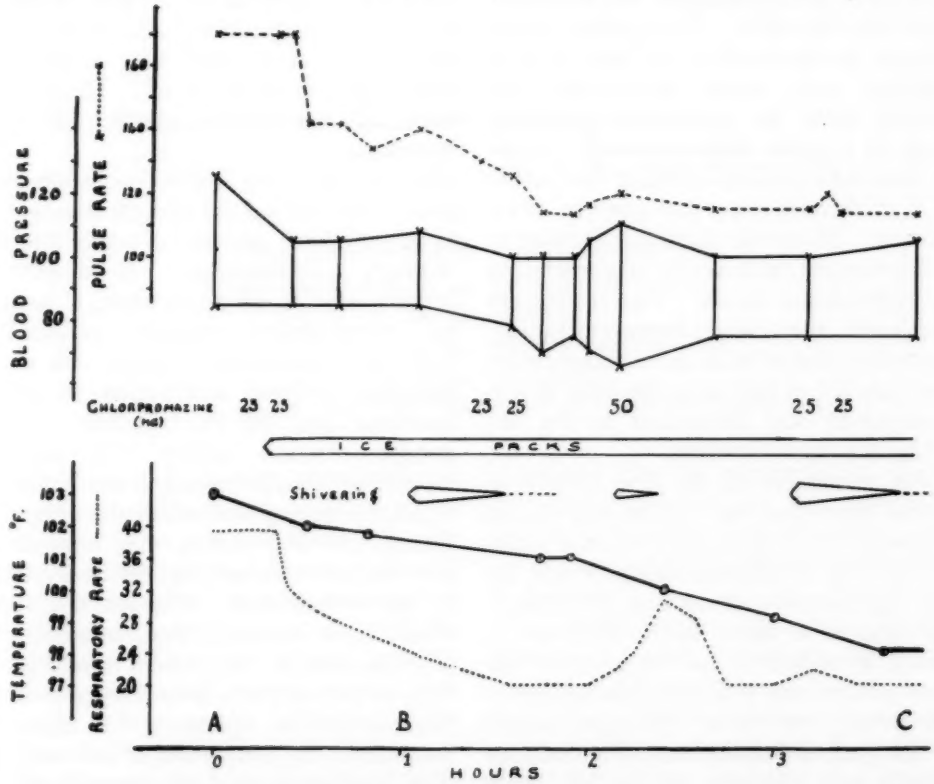

FIG. 2

Details of the second hypothermia.

rapidly, and parallel to this rise there was a deterioration in the state of consciousness until coma supervened. The left hemiplegia recurred and the right pupil became dilated and fixed. The second operation disclosed a massive oedema of the right hemisphere. The right frontal lobe was amputated to provide internal decompression and the dura and the bone flap were left unsutured, again for decompression. In addition to the original lesions there was now a widespread vascular embarrassment with which to contend and despite the extensive mechanical measures, there was no appreciable improvement after this operation. Therapeutic hypothermia was induced in the hope that, in reducing local tissue metabolism, the patient might be tided over the acute phase of vascular embarrassment. It can be deduced from figure 2 that this period of hypothermia was not entirely satisfactory. Shivering occurred frequently and prevented the lowering of temperature to hypothermic levels. The respiratory and pulse rates were, however, rapidly controlled and as soon as the temperature was reduced to normal an increase in responsiveness and movement in the left limbs was again observed.

On reconsidering the case history, it would seem that on the first and second occasions the hypothermia was not maintained over a sufficient length of time for this type of profound vascular disturbance. In contrast to these, at the third therapeutic hypothermia the temperature was well reduced and maintained at low levels for seventy-two hours. The improvement in the general responsiveness, oculomotor paresis and paralysis of the left limbs steadily progressed as the hypothermia continued. Within forty-eight hours she recovered consciousness sufficiently to open her eyes and occasionally to follow the examiner's activities (B, fig. 3). Five days later she began to respond to verbal commands and would open her eyes or grip the examiner's hand by request. Some movement even returned to the left fingers. She remained mute, however, although giving the impression of making an effort to speak, up to the time of her sudden and unexpected death. This took place twenty-eight days after the first operation and hypothermia and eighteen days after the third one had concluded. At post-mortem the extent of destruction of the right hemisphere was such that it is surprising that it had functioned at all. The actual cause of her sudden death was not apparent.

On the morning of the operation the patient was judged, by clinical standards, to be moribund and to be inoperable in ordinary circumstances. If desperate surgery were to be undertaken, it would be impracticable without artificially inducing hypotension. Despite the considerable cerebral destruction by haemorrhage and by the clipping of the middle cerebral artery, the rapidly recovering consciousness and the degree to which the hemisphere retained its physiological function during the immediate post-operative period can only be ascribed to the hypothermia. Without this, one would have expected that, immediately post-operatively, the patient would have been in the state which developed twenty hours after the operation, i.e. eighteen hours after the conclusion of the cooling. The standard surgical decompressive procedure did not produce any beneficial

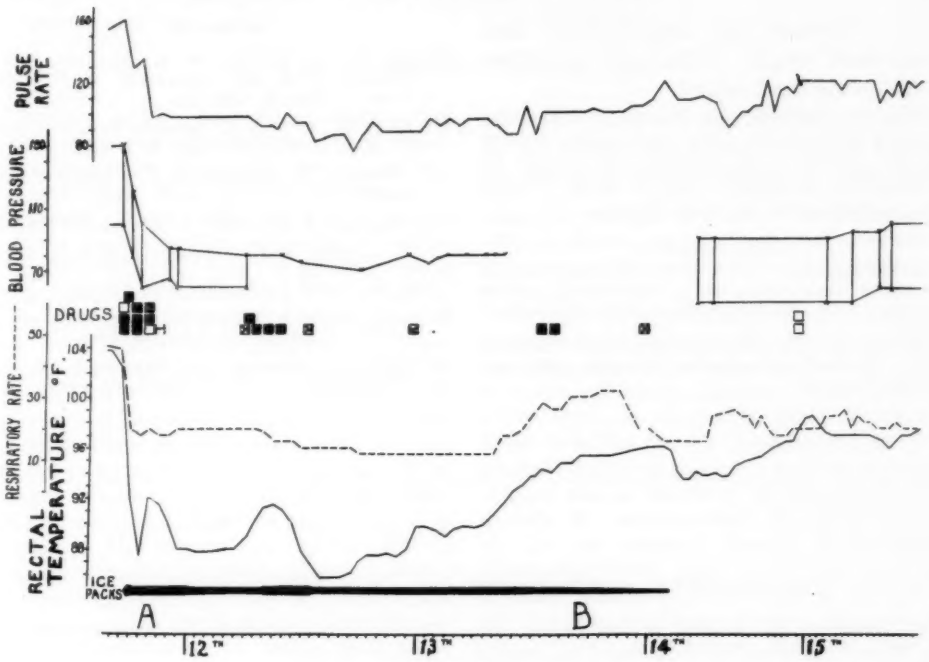

FIG. 3

Details of the third hypothermia and subsequent course.

Drugs: ■ represents 25 mg. chlorpromazine.
□ ,, 50 mg. pethidine.
▣ ,, 2 mg. l-methorphinan (Dromoran).
⊟ ,, 50 mg. hexamethonium.

All drugs were given by deep intramuscular injection with or without hyaluronidase.

effect. On two further occasions this patient was subjected to induced hypothermia while *in extremis*. In each of these there was a surprising degree of clinical improvement paralleling the reduction of the pulse and respiratory rates and of the temperature. Our observations certainly indicate that this improvement was directly related to the efficacy and the length of the cooling.

In this case the benefits derived from the induced hypothermia are so strikingly significant that the potentialities of this therapeutic measure are well worthy of further exploration. Two groups of cases would seem to lend themselves to this form of therapy:

(*a*) Intracranial ischaemic lesions, arterial or venous, in which the hypothermia is used in order to allow the brain to survive with a lowered metabolism, while the blood pressure would be maintained in the hope of opening up whatever channels of collateral circulation exist.

(*b*) Pyrexias of hypothalmic and brain-stem origin, either post-operative or following head injury.

Much experience is, however, still to be gained before hypothermia could be an established procedure apart from its use as a supplement to anaesthesia.

ACKNOWLEDGMENTS

We are indebted to Dr. A. Skene, Physician Superintendent of Walton Hospital, for referring this case to us, and to Dr. M. Wodzinski for the post-mortem report.

We are also grateful to the Sisters and Nurses of Walton Hospital whose kind co-operation made such a study possible.

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ANAESTHETIC APPOINTMENT AT GLASGOW UNIVERSITY

THE University of Glasgow in conjunction with the Western Regional Hospital Board has created a Senior Lectureship in Anaesthetics to organize and direct a Department of Anaesthetics at Glasgow University and Glasgow Royal Infirmary. This appointment carries the clinical ranking of Consultant.

The University and Regional Board has selected for this appointment Dr. Alex. C. Forrester.

Dr. Forrester is Chairman of the Anaesthetic Services Sub-Committee of the Central Consultants' and Specialists' Committee (Scotland), and is the Scottish representative of the British Medical Association Anaesthetic Group, London. He is a Consultant Anaesthetist at Glasgow Royal Infirmary, with which he has been associated for the past 18 years.

During that time, Dr. Forrester has participated in the clinical teaching of anaesthetics to medical students and post-graduates at the Infirmary. In the field of research Dr. Forrester has interested himself in the early introduction of curare into anaesthesia, and circulatory changes during anaesthesia.

He has taken time to visit many other Departments of Anaesthesia in this country and abroad, spending some time in the U.S.A. and Canada.

Dr. R. C. O. Saunders has been appointed Assistant to the above post.

Brit. J. Anaesth. (1955), **27**, 101.

ANNOTATION

THE RELIEF OF CHRONIC PAIN

COMBINING sedative or analgesic drugs which depress respiration with antidotes to their respiratory depressant action is by no means a new idea to anaesthetists. Soon after the introduction of thiopentone, Lundy (1935) described a method of minimizing respiratory depression by adding 25 mg. nikethamide to each 100 mg. thiopentone.

The synthesis of nalorphine in 1941 opened up a new field in the problem of producing relief of pain without respiratory depression. It was claimed that this drug would antagonize the central effects of opiates and the synthetic analgesics such as pethidine, amidone and levorphan. Eckenhoff, Hoffman and Dripps (1952) cast some doubts on its ability to antagonize the central action of analgesics, while Payne (1954) has shown that nalorphine potentiates the narcotic action of morphine. All workers are agreed that it antagonizes morphine-induced respiratory depression, although this effect may be transient and side effects, such as vomiting, are troublesome.

A recent addition to this field is levallorphan tartrate (1-3-hydroxy-N-allylmorphinan tartrate), which bears the same relationship to levorphan as nalorphine does to morphine. Reports suggest that it has many advantages over nalorphine. Hamilton and Cullen (1953) found it to be an effective antagonist to the respiratory depression produced by morphine, pethidine and levorphan. Their findings suggested that, although respiratory depression was abolished, some action of the analgesics persisted which enabled them to be used as effective supplements to nitrous oxide-oxygen anaesthesia.

Cullen and Santos (1954) have recently reported on the use of a combination of levorphan and levallorphan for the relief of chronic pain. When combined in a 4:1 ratio there was a loss of analgesia and many patients complained of symptoms similar to the acute abstinence syndrome. They found that a mixture of 8 to 10 parts levorphan with 1 part levallorphan resulted in no loss of the analgesic properties of the former and there was a significant increase in the minute volume of respiration as compared with the use of levorphan alone. This combination was administered to 18 patients with satisfactory results, although in a few cases it was followed by nausea and vomiting and all patients experienced a desire to sleep. Although their series is small the principle of mixing a potent analgesic with an effective antidote to its respiratory effects opens up great possibilities in the treatment of chronic pain.

In regard to the above combination it should be pointed out that there is some difference between the drug called "Dromoran" as referred to in American and British literature. In both countries the laevo form is now used, its generic designation being levorphan tartrate (1-methorphinan). The racemic form was originally used by American workers and is known as racemorphan hydrobromide (d-l-methorphinan). This latter has only one-half the analgesic potency of levorphan. Glazebrook (1952) found 1.5–2 mg. levorphan produced satisfactory analgesia in the majority of patients, but occasionally the dose had to be increased to 4 mg. It has the advantage of being longer lasting than morphine and is usually effective when taken by mouth.

Another new approach to the relief of chronic pain is the combination of analgesics with chlorpromazine. The latter has a leucotomy-like effect in large doses and also potentiates analgesic and hypnotic drugs. Satisfactory reports on this method have come from Sadove (1954), Howell, Harth and Dietrich (1954), and Dundee (1954). The latter claimed good results from a combination of 25 mg. chlorpromazine and 1.5 mg. levorphan given three to four times daily.

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Brit. J. Anaesth. (1955), **27**, 102.

A NEW VALVE FOR CONTROLLED RESPIRATION ANAESTHESIA

BY

A. R. RYAN

The Middlesex Hospital, London

THE soda lime absorption technique was introduced into clinical anaesthesia to remove the patient's carbon dioxide during spontaneous respiration anaesthesia (Waters, 1924). When controlled respiration anaesthesia was described under the name "ether apnoea" ten years later by Guedel and Treweek (1934), soda lime was again used to absorb the patient's carbon dioxide. The introduction of the costly gas cyclopropane at the same time (Waters and Schmidt, 1934) made the soda lime absorption technique essential. Because of its powerful central respiratory depressant effect, it was soon appreciated that cyclopropane was an aid to controlled respiration and was safer when employed in this manner (Guedel, 1940).

More recently the use of curare with cyclopropane or other anaesthetic agents has made the technique of controlled respiration anaesthesia relatively easy and widely used. Soda lime absorption of carbon dioxide continues, however, to be the only method employed in manual controlled respiration anaesthesia, even when cyclopropane is not used, as in the technique of curare, thiopentone, nitrous oxide-oxygen supplemented by pethidine or ether if necessary (Gray and Rees, 1952).

THE NON-RETURN EXPIRATORY VALVE

Against this background of the soda lime absorption of carbon dioxide, this paper will describe a simpler means of removing carbon dioxide together with the other expired gases by the use of a non-return expiratory valve (fig. 1). The use of a unit containing an expiratory valve and an inspiratory valve (non-return) is as old as anaesthesia itself; Morton's original draw-over inhaler contained these valves, as did Snow's facepiece. The idea is basic and at the present time similar valves are to be found in the "Oxford Vaporizer No. 1" (Macintosh and Mendelssohn, 1941). In America the Stephen-Slater (1948) non-rebreathing valve is widely used. They all, however, were designed primarily for use during spontaneous respiration anaesthesia.

The valve illustrated is designed for use during controlled respiration anaesthesia. It is a modification of the non-return expiratory valve on the "Oxford Vaporizer No. 1" and it can be seen that the new design simply provides a means of closing the expiratory valve quickly and effectively by a press-button. It is used with any continuous-flow machine with a reservoir bag. The addition of a press-button to expiratory valves is due to the

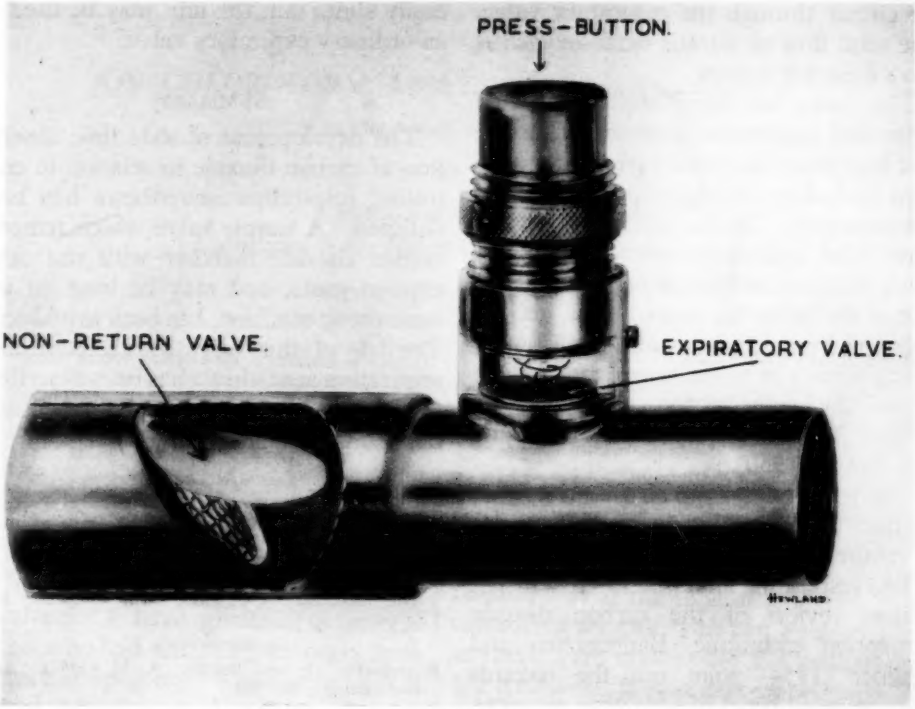

FIG. 1

work of Salt (1947), and this convenience has been increasingly added to anaesthetic equipment.

Mushin and Mapleson (1954) clearly pointed out the essentials of an ideal valve and the one under discussion compares favourably with their criteria. The expiratory valve is of the disc-and-pin type, with a light conical spring and exceptionally large expiratory ports to minimize resistance. The press-button, which contains a separate spring, pushes the disc on to its seating. The non-return valve is of thin rubber and is mounted so as to be easily removed if the unit is to be used as an ordinary expiratory valve.

USE OF THE VALVE

In order to use this new valve for controlled respiration, on a patient anaesthetized, curarized, and intubated, the valve is simply connected to the distal end of the concertina tubing of any Boyle's or continuous-flow machine, the new valve replacing the ordinary valve. The patient is inflated by closing the expiratory valve with the press-button and by squeezing the reservoir bag at the same time; the non-return valve during this period is open. Release of both the press-button and the reservoir bag allows expiration to occur; during this period the non-return valve is closed and all expired gases leave

the circuit through the expiratory valve. The total flow of nitrous oxide-oxygen is 6 to 8 litres per minute.

The valve has been used to provide controlled respiration anaesthesia for the past four years in a wide variety of operations including abdominal, thoracic, and neuro-surgery. In the latter case and in other head operations where the anaesthetic machine and anaesthetist are at the foot of the table, the press-button may be operated by a remote control attachment which screws on to the upper threads just below the press-button. The remote control is based on the work of Mushin and Ezard (1950).

The main advantage of the valve is its simplicity in providing an effective means of removing carbon dioxide during controlled respiration anaesthesia. In a recent critical review of the carbon dioxide absorption technique, Baumgarten and Betcher (1954) point out the hazards existing in all types of soda lime circuits: increased resistance, increased temperature of gases, exhausted soda lime, the accumulation of water vapour, and the dilution of gases. All of these are avoided by the non-return expiratory valve.

This non-return expiratory valve may also be used as a non-rebreathing valve during spontaneous respiration anaesthesia (Stephen and Slater, 1948). And by removing the non-return valve, which easily slides out, the unit may be used as an ordinary expiratory valve.

SUMMARY

The development of soda lime absorption of carbon dioxide in relation to controlled respiration anaesthesia has been outlined. A simple valve which removes carbon dioxide together with the other expired gases, and may be used on any anaesthetic machine, has been introduced. The use of this valve during controlled respiration anaesthesia has been described. Its advantages over the soda lime absorption technique have been stated.

ACKNOWLEDGMENT

I should like to express my thanks to Professor R. R. Macintosh, of the Nuffield Department of Anaesthetics, Oxford, for his kindness and encouragement during the preparation of this paper.

This valve may be obtained from A. Charles King Limited.

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ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.
Licentiate of the Royal College of Physicians

(*Continued from page* 46)

[The quantities used in Snow's work on $CHCl_3$ are cubic inches, grains and minims. As modern readers are not used to them, they have been translated into cubic centimetres on the following basis.
1 cubic inch = 16.38 c.c.
1 gramme of liquid $CHCl_3$ ≡ 200 c.c. of vapour at 20°C at 760 mm.
1 gramme = 15.43 grains, and so 1 grain ≡ 13 c.c. of vapour.
1 minim = .059 c.c. ≡ 17.6 c.c. vapour.]

Cerebral Disease. Affections of the head offer no obstacle to the administration of chloroform. I have given it to several patients who had suffered previously from an attack of apoplexy. Some of them still retained the paralysis resulting from their attack, but the chloroform has not been attended or followed by ill effects in any of these cases. The following case, in which alarming head symptoms had existed a few hours before the inhalation of chloroform, cannot fail to be interesting.

The 31st of October, 1854, was appointed by Mr. Fergusson to perform lithotrity on a gentleman, seventy-eight years of age, who had a phosphatic calculus in his bladder. He was a patient of Mr. Propert, and Mr. Fergusson had removed a similar calculus by lithotrity, and I had given him chloroform at each of the operations, and it was arranged that he should have chloroform on the present occasion. Mr. Propert informed Mr. Fergusson and me, on our arrival, that his patient had had an attack the night before resembling apoplexy; he had been insensible, the breathing had been stertorous, the pupils dilated, and the face very red and congested. Mr. Propert had caused him to be cupped to fourteen ounces, and had given him calomel in the course of the night, and in the morning he was as well as usual, and remained so at the time of our visit. We considered the case with Mr. Propert, and as there were reasons for not postponing the operation, it was determined that he should inhale the chloroform rather than be subjected to the pain. The vapour acted very favourably; he recovered his consciousness a few minutes after the operation, and expressed himself as feeling quite well.

Mr. Fergusson crushed another calculus in this patient in March 1855, when I again administered chloroform, and in 1856 I understood that he was free from the complaint.

Insanity. Chloroform acts on insane patients just as it does on others, that is to say, they are made insensible by it, and, when its effects are completely subsided, it leaves them in the same state of mind as before. Insane people are, however, often so suspicious that they cannot be persuaded to inhale chloroform, and it can

only be given to them by force. When once under its influence, however, I have seen teeth extracted, and other operations performed, which it would have been impossible to accomplish in the same individuals without resorting to inhalation. The use of chloroform in the treatment of mania will be alluded to in another part of this work.

Hard Drinkers. It was at one time alleged that hard drinkers of spirituous liquors were not susceptible of the influence of ether or chloroform, and for a long time there remained an impression that these persons were difficult to render insensible. I have always found that hard drinkers were rendered unconscious, and even comatose, by the same amount of ether or chloroform as other persons; but they sometimes have a morbid excess of sensibility in the nerves of common sensation, and do not lie still under the surgeon's knife except when the nervous centres are deeply narcotised, and the breathing almost stertorous. On this account, they sometimes inhale much more chloroform during a protracted operation than other persons.

AMOUNT OF VAPOUR OF CHLOROFORM ABSORBED TO CAUSE THE VARIOUS DEGREES OF NARCOTISM

Before proceeding to describe the mode of administering chloroform, it is desirable to treat of the quantity of it which produces its different effects. Without alluding to the facts and experiments which prove that all narcotics produce their effects by being absorbed into the circulating fluid, and so reaching the nervous system on which they act, it is only necessary to mention the following circumstances to show that this is the case as regards chloroform. In some experiments in which I assisted Dr. Sibson, we found that the vapour of chloroform produced its effects after both the pneumogastric nerves had been divided, exactly the same as before. Chloroform can be detected by means of chemical tests exhaling in the breath of those who have just previously inhaled it. It can also be detected in the urine after inhalation, and very readily in all the tissues of animals that have been killed by it, for several days after death.

The quantity of chloroform in the blood in the different degrees of narcotism might be estimated approximately from the amount used in inhalation, but I devised some experiments in 1848 for ascertaining the quantity with accuracy.* The experiments were based on the following circumstances.

When air containing vapour is brought in contact with a liquid, as water or serum of blood, absorption of the vapour takes place, and continues till an equilibrium is established; when the quantity of vapour in both the liquid and air, bears the same relative proportion to the quantity which would be required to saturate them at the temperature and pressure to which they are exposed.

This is only what would be expected to occur; but I verified it by numerous experiments in graduated jars over mercury. The intervention of a thin animal membrane may alter the rapidity of absorption, but cannot cause more vapour to be transmitted than the liquid with which it is imbued can dissolve. The

* Medical Gazette, vol. xli-ii.

temperature of the air in the cells of the lungs and that of the blood circulating over their parietes is the same; and, therefore, when the vapour is too dilute to cause death, and is breathed till no increased effect is produced, the following formula will express the quantity of any substance absorbed: —As the proportion of vapour in the air breathed is to the proportion that the air, or the space occupied by it, would contain if saturated at the temperature of the blood, so is the proportion of vapour absorbed into the blood to the proportion the blood would dissolve.

The manner in which the experiments were performed, was to place a small animal in a glass jar, so large that it formed a capacious apartment for it, and held much more air than it would require in the course of the experiment. The jar was covered with a closely-fitting lid, and a carefully-weighed portion of chloroform was allowed to diffuse itself through the air of the jar. The experiments were continued till the chloroform produced no further effect. I shall pass over a number of tentative experiments, and adduce only a few of those which were made after I had ascertained the quantities requisite to produce the desired effect. The results obtained in these experiments were entirely due to the degree of dilution of the vapour; for the quantity of chloroform employed was, in every instance, more than would have killed the animal in a much shorter time than the experiment lasted, if it had been conducted in a smaller jar. It is assumed that the proportions of vapour and air remain unaltered during the experiment; for the quantity absorbed must be limited to what the animal can breathe at the time, which is so small a part of the whole that it may be disregarded.

Experiment 1. A guineapig and a white mouse were placed in a jar holding 3,000 cubic inches, and fifteen grains of chloroform (0.4%) were introduced by a tube in the lid of the jar, which was closed immediately by a screw. The chloroform fell on some blotting paper suspended in the jar, and in a minute or two was converted into vapour and diffused through the air in the jar. The animals were allowed to remain half an hour, and were unaffected by the chloroform, except that they appeared to be a little less brisk than usual, during the first two or three minutes after their removal.

Experiment 2. A guineapig was placed in the same jar, and twenty-two and a half grains of chloroform were introduced in the same manner as before, being three-quarters of a grain to each hundred cubic inches of air (0.595%). In two or three minutes the chloroform was converted into vapour and diffused through the air in the jar. Six minutes afterwards the guineapig began to stagger, and soon afterwards was unable to keep on its legs. It was kept for half an hour in the jar, but did not become further affected. It was occasionally quiet, but always tried to walk when disturbed by moving the jar. When taken out, it flinched on being pricked, and tried to walk, although unable to support itself on its legs. It recovered from the effects of the chloroform in three or four minutes.

Experiment 3. Another guineapig was placed in the same jar, and thirty grains of chloroform (0.79%) were introduced. In three or four minutes the chloroform had evaporated and diffused itself through the air in the jar. In two minutes afterwards

the guineapig lay down, but stirred when the jar was moved. It was allowed to remain in the jar for half an hour, being asleep except when disturbed. When taken out it awoke and endeavoured to walk, but was unable to support itself at first. It flinched on being pricked. Recovered in three or four minutes.

Experiment 4. A cat was placed in the same jar, and the same quantity of chloroform was introduced. In three minutes it had evaporated, and, when ten minutes had elapsed, the cat began to stagger. Soon afterwards it was unable to support itself on its legs; and, when a quarter of an hour had elapsed, it seemed asleep, but raised its head when the jar was inclined. It remained apparently sleeping till the end of an hour, when it was taken out. It was unable to stand, but was sensible to the slightest pinch. It recovered gradually in the course of twenty minutes.

Experiment 5. Sixteen grains of chloroform were put into a jar holding 1,600 cubic inches, being one grain to each 100 cubic inches of air (0.8%), as in the last two experiments. When it was converted into vapour, a white mouse was introduced by moving the lid a little to one side for a moment. After running about for a minute and a half, it began to stagger and to lose power, but it continued to run with little intermission till three minutes had expired. After this it lay still, except when the jar was inclined, when it always endeavoured to maintain its balance and to walk. It also moved its limbs now and then, when not disturbed. It was removed at the end of ten minutes, when it tried to walk, but was unable. It did not flinch when its tail was pinched, but flinched, half a minute after its removal, on one of its toes being pinched. It recovered in two or three minutes.

Experiment 6. A guineapig was placed in the jar holding 3,000 cubic inches, and 37.5 grains of chloroform were introduced in the same manner as in the former experiments, being a grain and a quarter to each 100 cubic inches of air (1%). The chloroform took three or four minutes to evaporate and diffuse itself in the jar; and by the end of this time the guineapig, which had been excited and running about, began to stagger, and in two minutes longer it was unable to walk, but endeavoured to keep its balance when the jar was inclined. At the end of a quarter of an hour it was lying still, but moved its limbs when it was rolled over by inclining the jar; but it made no voluntary effort. It was taken out when thirty-three minutes had elapsed. It moved its limbs as it was removed, though apparently not in a voluntary manner. Its limbs were not relaxed. It was quite insensible to pricking. It recovered in about ten minutes. The temperature in the axilla before it was put into the jar was 100° Fah., and immediately after its removal 96°.

Experiment 7. A guineapig was placed in the same jar, and forty-five grains of chloroform were introduced, being a grain and a half to each 100 cubic inches of air (1.2%). In four minutes after the chloroform had evaporated, the guineapig was unable to walk. In half a minute more it seemed asleep, but there was a tremulous motion of the hind legs, which continued till ten minutes had elapsed. Afterwards it lay still, but winked now and then spontaneously. When rolled over by moving the jar, it made no voluntary effort. It

was taken out twenty minutes after the chloroform had evaporated. It winked spontaneously, and also when the eyes were touched. It did not flinch when the ear was pricked, but flinched when the paw was pricked. The temperature in the axilla before the experiment was 100°, and immediately afterwards it was 96°. The guineapig recovered from the effects of the chloroform in ten minutes.

Experiment 8. A guineapig was put into the same jar, and 52.5 grains of chloroform were introduced, being a grain and three-quarters to each 100 cubic inches of air (1.4%). The chloroform evaporated in the course of four minutes, at the end of which time the guineapig was altered in its manner, as if partially inebriated. In two minutes more it was becoming drowsy. A little while afterwards it was lying down. Six minutes after the evaporation of the chloroform was complete, the guineapig made no effort when turned over by inclining the jar, but only moved its feet, as it were automatically. At the end of nine minutes, it was lying quietly and breathing naturally. When fifteen minutes had elapsed it was in the same condition, and was removed from the jar. It cried and flinched on the foot being pricked. The temperature in the axilla was 97°. In five minutes after its removal it was fast recovering, and in ten minutes was quite recovered.

Experiment 9. A guineapig was placed in the jar used in the last three experiments, and sixty grains of chloroform were introduced in the same manner, being two grains to each 100 cubic inches of air (1.6%). In four minutes it was all converted into vapour, and the guineapig was beginning to be affected by it. In two minutes more it was unable to stand or walk. In five minutes from the time when the evaporation was complete, the guineapig showed no sign of sensibility when turned over by inclining the jar; the breathing was natural. At the end of ten minutes it was lying still, breathing gently forty times in the minute. At the end of fifteen minutes it was in the same condition. From seventeen to twenty minutes, it stretched out one of its hind legs several times, and was doing so when taken out, at the end of twenty minutes. It showed no sign of sensibility when pricked. The temperature in the axilla was 96°. It began to recover gradually in a minute or two, and recovered completely in from ten to fifteen minutes.

Experiment 10. A cat was placed in the same jar, and the same quantity of chloroform was introduced in the same manner. It became quite insensible in a few minutes after the chloroform was introduced; and it was allowed to remain for twenty-five minutes when it was taken out. It was perfectly insensible to pricking, and its muscles were quite relaxed; it was breathing gently, and the pulsations of the heart were between sixty and seventy in the minute. It was immediately made the subject of another experiment of drowning whilst insensible, which need not be related in this place.

Experiment 11. Four grains of chloroform were put into a glass jar holding 200 cubic inches (1.6%), and when it had evaporated and was diffused through the air in the jar, a white mouse was introduced by momentarily removing the cover a little to one side. A minute after its introduction the mouse was lying, but it moved its legs for a quarter of a minute longer.

When four minutes had elapsed, the breathing became slow, and it was taken out. It was totally insensible for the first three minutes after its removal, and recovered during the two following minutes.

Experiment 12. Thirty-two grains of chloroform were diffused through the air of a jar holding 1,600 cubic inches, being two grains to each 100 cubic inches (1.6%) as in the last three experiments. A white mouse was introduced by moving the cover a little to one side for a moment. In one minute it was insensible, and did not make any effort on being rolled about by inclining the jar, but it moved its paws for half a minute longer. It remained insensible, breathing 160 times in the minute, till it was taken out at the end of five minutes. It was quite insensible to pinching. It began to walk in a minute or two. Its temperature before the experiment was 98°, and immediately afterwards was 92°. The temperature of the room was 68°.

Experiment 13. A guineapig was put into a jar holding 3,000 cubic inches, and 67.5 grains of chloroform were introduced on blotting paper suspended within the jar, being $2\frac{1}{4}$ grains to each 100 cubic inches (1.8%). In four minutes, the chloroform had all evaporated, and the guineapig was becoming affected. In two minutes more, it was quite insensible. Eight minutes after the chloroform had evaporated, it was lying still, breathing forty times in the minute. During the next three or four minutes, it moved one or other of its legs occasionally. At the end of seventeen minutes, it was lying still, and the breathing was twenty-six in the minute. It was taken out at the end of twenty minutes quite insensible; in three or four minutes it began to try to walk, and in ten minutes, was quite recovered.

Experiment 14. Two white mice, one being full grown, and the other about three-quarters grown, were placed in the jar holding 1,600 cubic inches, and forty grains of chloroform were introduced on blotting paper, being two grains and a half to each hundred cubic inches (2%). In two minutes, the chloroform had evaporated, and the mice were much excited. In another minute, they were unsteady in walking; and in a minute more, the old mouse was lying insensible, and breathing deeply and laboriously. In four minutes more, *i.e.*, six minutes after the chloroform had evaporated, the young mouse was insensible also, but was moving one of its hind legs. In another four minutes, the young mouse was breathing by slow gasps, whilst the old one continued to breathe deeply as before. Three minutes later, *i.e.*, thirteen minutes after the chloroform had evaporated, the old mouse had begun to gasp, and the young one was gasping only at intervals. They were removed, and recovered completely in ten minutes. The young one recovered most quickly. Their temperature, on being removed, was about 90°.

(To be continued)

Elements of Pediatric Anesthesia. By C. R. Stephen. Published by Blackwell Scientific Publications Ltd., 1954. Pp. 109; 25 illustrations. Price 25*s*.

This is a good little book and its contents fulfil the promise of its title; that is, they lay more emphasis on principles than on technique. It should help the occasional paediatric anaesthetist to avoid the grosser pitfalls, and some of the views expressed will be of interest to those whose work is largely in this field.

There are excellent chapters on the physiology of the child in relation to anaesthesia and on premedication, both of which are as complete as might be expected in a book of this size. The views expressed on premedication are sound and the attitude adopted towards basal narcosis is realistic.

It is not uncommon for the British reader of American text-books of anaesthesia to find much with which he cannot agree, but in this case the author's views, with one notable exception, coincide quite closely with current views, as is shown by the sections on endotracheal intubation and on the use of thiopentone. The author emphasizes that in the past, dangers of endotracheal intubation of children have been overstressed, and advocates the much wider use of this procedure; his views are supported by very convincing figures. He also says that thiopentone induction is not contra-indicated in any child where venepuncture is practicable. There is another section in which it is stated that the anaesthetic drugs are administered with three principal objectives in mind: (*a*) Hypnosis, (*b*) Analgesia, and (*c*) Relaxation. This also is a concept familiar in Great Britain.

The British reader will perhaps be surprised at the section on curariform drugs, in which it is stated that the effective dose of tubocurarine (which is the only relaxant drug mentioned) is 1 mg. per 15 lb. (6.6 kg.) body weight and that the employment of this drug in children under three is questionable. The use of this order of dosage is likely to increase rather than diminish the difficulties of anaesthetizing young children, in that it produces a type of respiration which results in quite inadequate ventilation and is difficult to control. There is, however, little else to criticize.

The production of the book is good; in common with the other numbers in this American Lecture Series, it is well printed on excellent paper and has the familiar, rather elegant, black leatherette cover. It will satisfactorily fill the hiatus in anaesthetic literature until such time as a comprehensive work on paediatric anaesthesia is published, and deserves to be widely read.

J. G. Rees

Heart. A Physiologic and Clinical Study of Cardio-vascular Diseases (2nd edition). By Aldo A. Luisada. Published by Baillière, Tindall and Cox, Ltd., 1954. Pp. 680; 312 illustrations. Price £5 14*s*.

The work might be described, without any intention of deprecating its value, as an elementary text-book on the heart and circulation. It is designed to interest, and one might add to help, those whose principal study is not in cardiology, but who in one way or another find themselves dealing with cardiac patients. It is a manual of descriptive value particularly written and illustrated to demonstrate the subject in the widest sense, so that there are good chapters on the development and normal physiology of the cardiovascular system, besides a most comprehensive section on the technical study of the cardiac patient, which deals with everything from phonocardiography to the measurement of circulation time. The bulk of the work deals with diseases of the heart and vessels. The style is simple and the arrangement excellent, so that facts are easily found and understood, while great care has been taken with the figures, each of which eliminates unnecessary repetitive text.

The excellence of the work lies primarily in the direct and opinionative manner in which the subject matter is dealt with, leaving the reader with a clear impression of the subject and the

author's views. However, this might be construed as a weakness since more specialized workers will search in vain for detailed discussion on some subjects. The few paragraphs on anaesthesia, of necessity only a very small part of the book, do little more than deal with principles, though some of the statements would be queried by anaesthetists in this country.

The book should be useful to anyone wishing to increase his knowledge of heart disease. It is beautifully produced, is up to date for a large textbook, and is well referenced from the world literature.

W. D. Wylie

CORRESPONDENCE

Sir,—In the Educational Supplement of your November issue I wrote a model "Question and Answer" paper on the subject of explosions during surgical operations under anaesthesia. In the last paragraph I mentioned that the inert gas Argon had rather unexpectedly proved to be possessed of anaesthetic properties. In my original notes for this paper I was more accurate and mentioned that it was Xenon which was being investigated in this respect.

Mr. F. W. B. Kittel, of the Medical Division of the British Oxygen Co. Ltd., kindly pointed out this error to me, giving me certain interesting information: first that as far as his firm can ascertain Argon appears to be physiologically as inert as nitrogen and helium, and also that Xenon, although it has anaesthetic properties, is so rare and costly to extract that it is unlikely ever to be of any value as an anaesthetic agent.

I would be grateful if you could print this letter so that the error which crept into my article in the latter stages of its development shall not be perpetuated.

A. H. GALLEY,
King's College Hospital.

FACULTY NEWS

THE following, having successfully completed both parts of the examination, have been awarded the Fellowship in the Faculty of Anaesthesia of the Royal College of Surgeons.

Barr, Margaret Nina	Milner, R. W.
Cass, N. M.	Morris, D. D. B.
Faull, Rosemary Agatha	Nobes, P. J.
Gillinson, R. S.	Oliver, F. W.
Hamlyn, D. D.	Rahaman, Shaikh Abdur
Kasian, Aram Hovsep	Thomas, E. T.
Mathews, E. T.	Wilson, Sheila Margaret

BOARD OF FACULTY ELECTION

UNDER the Constitution of the Board, three Fellows and one Member retire annually in rotation.

The Board consists of:

(*a*) The President and Vice-Presidents of the College (*ex officio*).

(*b*) Eighteen Fellows representing the Fellows of the Faculty.

(*c*) Three Members representing the Members of the Faculty.

Dr. K. G. Lloyd Williams, Dr. B. L. S. Murtagh, and Dr. Vernon F. Hall, representing the Fellows, and Dr. A. J. W. Beard, representing the Members, are retiring this year in rotation; all are applying for re-election, Dr. Beard this time as a Fellow.

The election will take place at the College on Wednesday, March 16, 1955, at 3.30 p.m., and the following have applied for election to represent the Fellows.

Beard, A. J. W.	Lloyd Williams, Katherine Georgina
Belam, O. H.	McConnell, W. S.
Boyle, A. K.	Murtagh, B. L. S.
Cope, R. W.	Parry Brown, A. I.
Crawford, J. H.	Pinkerton, H. H.
Galley, A. H.	Sandiford, H. B. C.
Hall, V. F.	Woodfield Davies, H.
Harbord, R. P.	

MEMBERS

No application has been received from any Member of the Faculty for Election to the Board, and there will therefore be two vacancies on the Board for the year 1955–56, and three vacancies will occur at the next Election in March 1956.

Printed in Great Britain by JOHN SHERRATT & SON, Park Road, Altrincham